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14th Annual Report

National Institutes of Health Program in Biomedical and Behavioral Nutrition Research and Training

Fiscal Year 1990

U.S. Department of Health and Human Services
Public Health Service
National Institutes of Health

14th Annual Report

National Institutes of Health Program in Biomedical and Behavioral Nutrition Research and Training

Fiscal Year 1990

NIH Nutrition Coordinating Committee
Division of Nutrition Research Coordination

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EXECUTIVE SUMMARY

Nutrition research represents a cross-cutting scientific endeavor that seeks to assess the consequences of food or nutrient intake in the intact organism and the metabolic and behavioral mechanisms involved. As such, it encompasses studies at the cellular and subcellular levels; elucidation of the metabolic function of nutrients in both animals and humans; examination of genetic-nutrient-environmental interactions; and studies of the role of diet in the maintenance of health and the prevention of disease in humans, including clinical trials, epidemiological studies, metabolic studies, surveillance, and nutritional status monitoring studies. All of these are activities of the NIH Program in Biomedical and Behavioral Nutrition Research and Training.

Over the past 14 years, this report, published annually since 1977, has emphasized the coordination of nutrition research at NIH, the activities of the NIH Nutrition Coordinating Committee (NCC), the highlights of the nutrition research program and associated program development, and the fiscal year obligations in nutrition research and training. These topics also are featured in this year's report detailing highlights of nutrition research at NIH and the activities of the NCC.

The NCC was established in 1975 in the NIH Office of the Director, in recognition of the importance of nutrition as a cross-cutting issue at NIH. In FY 1990, the NCC consisted of representatives from 13 NIH institutes and 4 centers, with liaison representatives from other NIH offices, as well as from other Federal agencies. Since 1988, the NCC has been part of the Division of Nutrition Research Coordination (DNRC) in the Office of the Director. The DNRC was created to firmly establish the trans-NIH coordination of nutrition research and training as a permanent and identifiable position within the NIH and to recognize the additional responsibilities acquired over time by the NCC office. The NIH nutrition program continues to be coordinated through the NCC, which operates as an NIH-wide forum and locus for the coordination of research efforts, helping the NIH to avoid duplication of effort, and to speak with one voice in nutrition matters. The NIH collaborates with other U.S. government organizations, both within and outside the Department of Health and Human Services (DHHS); with academic institutions; with the private sector and the public; and with investigators in other countries who are developing and implementing research programs of mutual interest. Fostering cooperation and collaboration in nutrition research and training within the NIH is a major function of the DNRC and its NCC. The coordinated trans-NIH activities, as well as the collaborative interagency activities at the DHHS and Federal levels, of the NCC and DNRC are detailed in section 1 and the appendices of this report.

Each institute, center, and division (ICD) of the NIH plays a unique role in support of nutrition research, as each funds those areas of nutrition science related to its own particular research mission. The combination of the research areas thus represented encompasses the entire spectrum of modern biomedical nutrition research, from basic to applied, providing a diversity which is one of the NIH's greatest assets. Descriptions of the individual ICD nutrition research programs are presented in section 2, together with descriptions of the nutrition-related activities of several of the NIH liaison organizations represented on the NCC.

This report is not designed to give a comprehensive description of each of the approximately 2,400 nutrition research and training projects supported by the NIH during FY 1990. However, we have tried to convey the range and diversity of these projects by presenting selected research highlights which involved peer-reviewed studies funded by many different institutes in section 3 of this report. Research related to the nutrition priority area objectives of *Healthy People 2000: National Health Promotion and Disease Prevention Objectives* is highlighted. Such research encompasses prevention of some of the most common nutrition-related disorders affecting our population--obesity, coronary heart disease, cancer, and osteoporosis--and the study of nutrition throughout the life cycle--for example, in maternal and child health and in aging. In addressing these topics, special attention is directed towards women and minorities, groups that are disproportionately affected by nutrition-related disorders. Other topical areas of research highlighted include nutrition and neurological function, dietary restriction, nutrition and molecular biology, and diet and nutrition in acute and chronic illness and injury. The interdisciplinary and collaborative nature of nutrition research is emphasized in reports on research conducted within the Clinical Nutrition Research Units, the General Clinical Research Centers Program, other centers and programs. National nutrition monitoring research, technology transfer activities, and training programs with nutrition components also are highlighted.

Finally, information on the fiscal year obligations in nutrition research and training is provided in section 4. In FY 1990, as in previous years, the NIH led all Federal agencies in financial support of biomedical nutrition research and training, for a total of $292 million. The NIH expenditures have consistently represented between 70 and 73 percent of all Federal expenditures and between 92 and 95 percent of all DHHS expenditures in biomedical nutrition research and training. The NIH expenditures for nutrition research and training have increased steadily during the past decade, growing from $139 million in FY 1980 to $292 million in FY 1990. This represents an increase of 110 percent (or 17 percent if dollars are adjusted for inflation). The NIH nutrition research and training dollars have consistently represented approximately 4 percent of total NIH obligations since 1977.

Important discoveries over the last decade in molecular biology, genetics, and immunology have provided new opportunities for advances in the biomedical sciences. The techniques for addressing the fundamental questions about the nature of living organisms that have evolved from these discoveries are now beginning to be applied to nutritional studies. Their further application should advance biomedical nutrition research at an unprecedented pace and have a major impact on health.

ACKNOWLEDGMENTS

The activities of the NIH Nutrition Coordinating Committee (NCC) would not be possible without the support and commitment to nutrition research of the institute, center, and division (ICD) members and alternates and the liaison representatives to the committee. Each year, the representatives to the NCC and other NIH staff devote personal time and effort over and above their full-time ICD responsibilities to make this annual report possible. The following individuals deserve special acknowledgment for their contributions this year: Dr. Peter Greenwald, Dr. Carolyn Clifford, and Dr. Mark Messina, NCI; Nancy Ernst, Karen Donato, and Dr. Abby Ershow, NHLBI; Dr. Joseph Ciardi and Dr. Joan Wilentz, NIDR; Dr. Van Hubbard, NIDDK; Patricia Turner, NINDS; Dr. Eugene Zimmerman, NIAID; Dr. Yvonne Maddox, NIGMS; Dr. Ephraim Levin, NICHD; Dr. Barbara Underwood and Terrence Gillen, NEI; Dr. Thorsten Fjellstedt and Dr. Michael Galvin, NIEHS; Dr. Ann Sorenson, NIA; Dr. Joan McGowan, NIAMS; Dr. Jack Pearl, NIDCD; Dr. Harriet Gordon, NCRR; Dr. Kenneth Bridbord and Dr. Ferdinand Hui, FIC; Dr. John Chah and Dr. June Lunney, NCNR; Pamela Lokken and Joyce Rudick, NCHGR; Gloria Stables, CC; Judy Mahaffey and Charles Twigg, DCRT; Betsy Duane, DLA; and Dr. Sooja Kim, DRG.

The timely publication of this report would not have been possible without the extraordinary cooperation and assistance of the many individuals from Editorial Operations Branch, DPI, OC; Printing and Reproduction Branch, DTS, ORS; Administrative Office staff, OD; and many other individuals at the NIH who made special efforts for this report.

On behalf of the NCC members I wish to thank the staff of the Division of Nutrition Research Coordination (DNRC) for their contributions in the preparation of this report. Special acknowledgments are due to Dr. Susan Pilch for coordinating the development and overseeing the production of this annual report, including drafting portions of the report and conducting the data analyses included in it. Thanks also are due to Ellen Mirin for her outstanding editing and production assistance, to Nancy Gaston for her careful review of the document, and to Margaret Murphy for her excellent secretarial support.

Darla E. Danford, M.P.H., D.Sc.
Chairperson
NIH Nutrition Coordinating Committee
Director
Division of Nutrition Research Coordination

Section 1. Coordination of Nutrition Research and Training

COORDINATION OF NUTRITION RESEARCH AND TRAINING

NIH'S INVESTMENT IN NUTRITION RESEARCH

The mission of the NIH is to improve the health of the nation by increasing the understanding of processes underlying human health, disability, and disease; advancing knowledge concerning the health effects of interactions between humans and the environment; and developing and improving methods of preventing, detecting, diagnosing, and treating disease. To carry out its mission and legislative mandates, the NIH currently is organized into an Office of the Director, 13 research institutes, 2 service divisions (Division of Research Grants and Division of Computer Research and Technology), 5 centers (the Clinical Center, the Fogarty International Center, the National Center for Nursing Research, the National Center for Human Genome Research, and the National Center for Research Resources), and the National Library of Medicine. Figure 1 shows the components of the NIH.

The NIH's commitment to biomedical nutrition research is reflected by the unique contribution each institute, center, and division (ICD) makes in support of nutrition research related to its own particular mission. As a whole, these research efforts encompass the entire spectrum of nutrition research, ranging from determining individual nutrient requirements of the cell to identifying diet and risk factors for diseases. NIH's primary nutrition mission lies in biomedical and behavioral research and training, but also supports nutrition education and technology transfer as integral parts of many research programs.

Through these components, the NIH is the major agency within the Federal government that supports research and training in nutrition as it relates to health maintenance, disease treatment and prevention, and human development throughout the life cycle. In FY 1990, the NIH led all Federal agencies in financial support of nutrition research and training for a total of $292 million. The legislative authority for nutrition at the NIH is presented in appendix A.

DIVISION OF NUTRITION RESEARCH COORDINATION

An important addition to the NIH organization was the establishment in 1988 of the Division of Nutrition Research Coordination (DNRC) within the Office of Disease Prevention (ODP), Office of the Director (OD), as shown in figure 2. The new division enhanced and expanded NIH's goals to coordinate nutrition research programs and training, avoid duplication of research efforts among ICDs, and present nutrition information uniformly. The DNRC advises the Director of the NIH and the Associate Director for Disease Prevention on nutrition research. The DNRC represents the NIH at the department and interagency level on committees addressing nutrition research and nutrition policy issues.

The coordination activities by the DNRC involve three major categories: coordinated trans-NIH activities; collaborative interagency activities at the DHHS level; and collaborative interagency activities at the Federal level. At the NIH level, the DNRC coordinates nutrition activities through the Nutrition Coordinating Committee (NCC) and its Nutrition Education Subcommittee (NES). The DNRC also relies extensively on the expertise of these two committees in its collaborative nutrition activities at the DHHS and Federal level.

Coordination of Trans-NIH Activities

NIH Nutrition Coordinating Committee - NCC

The NCC, established in 1975, operates as an NIH-wide forum and locus to review, stimulate, and encourage the support of nutrition research and training in order to better define the role of nutrition in the promotion and maintenance of health and in the prevention and treatment of disease. The functions and responsibilities of the NCC now are encompassed within the framework of the DNRC.

Currently, the NCC consists of representatives from 13 institutes and 4 centers at the NIH.

Figure 1. Components of the National Institutes of Health

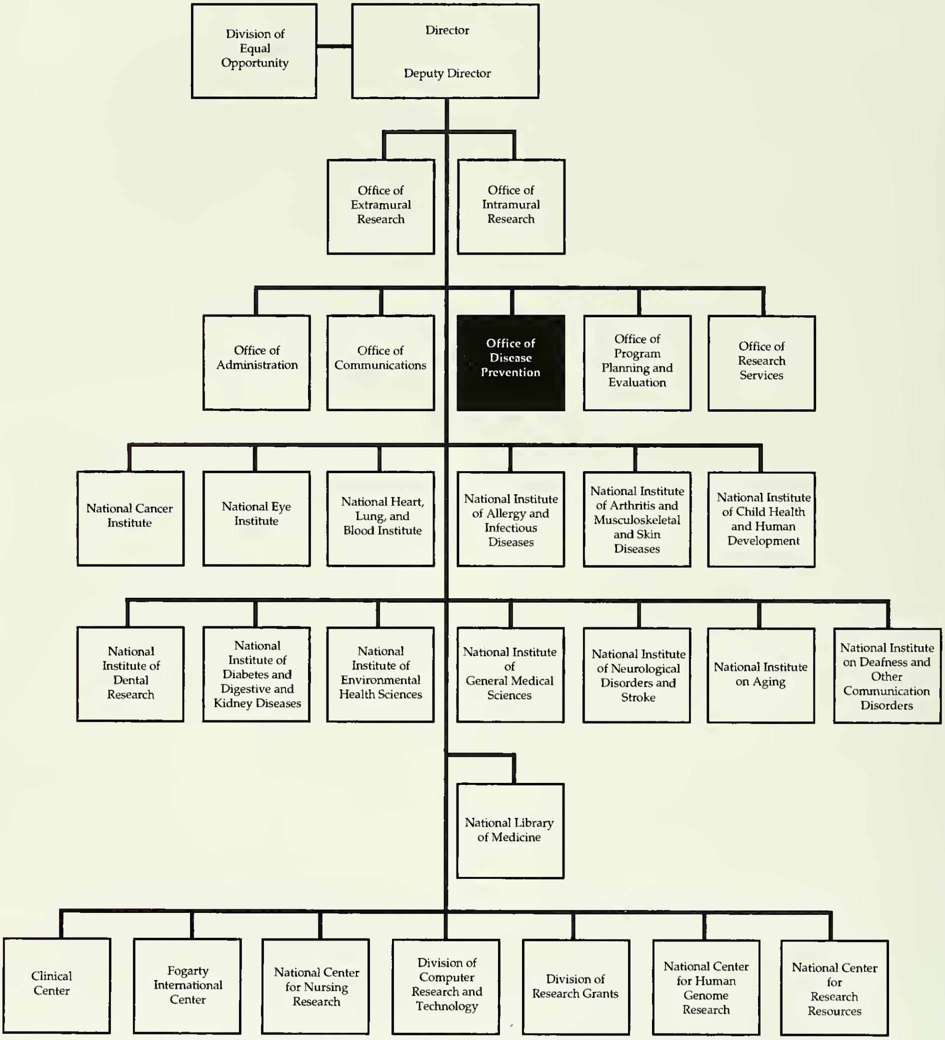
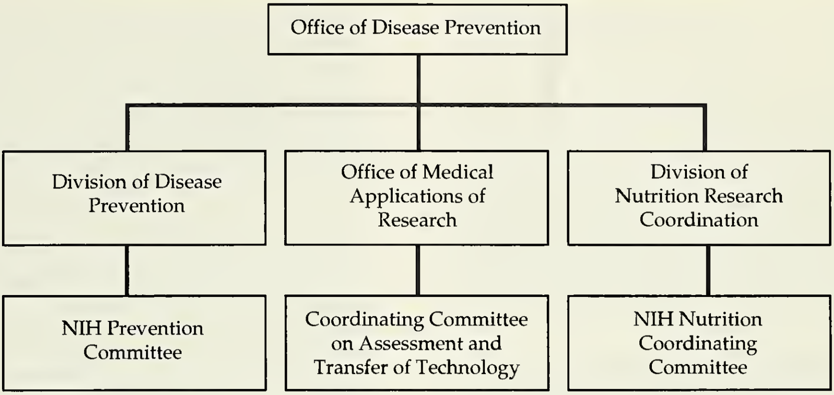

Division of Equal Opportunity
Director
Deputy Director
Office of Extramural Research
Office of Intramural Research
Office of Administration
Office of Communications
Office of Disease Prevention
Office of Program Planning and Evaluation
Office of Research Services
National Cancer Institute
National Eye Institute
National Heart, Lung, and Blood Institute
National Institute of Allergy and Infectious Diseases
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Child Health and Human Development
National Institute of Dental Research
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute of Environmental Health Sciences
National Institute of General Medical Sciences
National Institute of Neurological Disorders and Stroke
National Institute on Aging
National Institute on Deafness and Other Communication Disorders
National Library of Medicine
Clinical Center
Fogarty International Center
National Center for Nursing Research
Division of Computer Research and Technology
Division of Research Grants
National Center for Human Genome Research
National Center for Research Resources

Figure 2. Components of the Office of Disease Prevention


Office of Disease Prevention
Division of Disease Prevention
Office of Medical Applications of Research
Division of Nutrition Research Coordination
NIH Prevention Committee
Coordinating Committee on Assessment and Transfer of Technology
NIH Nutrition Coordinating Committee

Additional NIH offices and other agencies of the Department of Health and Human Services and U.S. Department of Agriculture (USDA) have liaison representatives to the committee. Lists of NCC members, alternates, and liaison representatives, and members of the NCC Nutrition Education Subcommittee, Obesity Work Group, and NIH Task Force on the Nutrition Priority Area Year 2000 Health Objectives for the Nation as of September 1, 1990, can be found in appendix B.

The NCC provides a locus for the review and coordination of research and training efforts related to nutrition and for the development of the NIH Program in Biomedical and Behavioral Nutrition Research and Training. The NCC has published an annual report of this program since 1977. The description of NIH-wide activities contained herein constitutes the *14th Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training, FY 1990* (NIH Publication No. 91-2092, 1991). The NCC forum minimizes the duplication of effort among the institutes and identifies areas where research training and development can be enhanced. This is accomplished through several different approaches, such as developing program announcements (PAs), requests for applications (RFAs), and requests for proposals (RFPs); appendix C lists PAs, RFAs, and RFPs in nutrition published in FY 1990.

The NCC plays a key role in the development of nutrition research policy at the NIH. Currently, NIH's nutrition research policy consists of eight areas. Research is emphasized in four of these areas: clinical nutrition throughout the life cycle, and nutritional factors in the development of disease, prevention of disease, and treatment of disease. The other four areas are related to education and technology transfer: the transfer of modern nutrition technology, nutrition education for professionals and the public, nutrition research training and research manpower development in nutrition, and trans-NIH and interagency coordination.

The DNRC and its NCC prepare and review many trans-NIH and interagency nutrition-related documents. In FY 1990, the DNRC and its NCC prepared and published the updated brochure *Nutrition Research at the NIH* (NIH Publication No. 90-2611, 1990) that provides descriptions of nutrition-related biomedical research programs of the institutes and centers to inform extramural investigators and potential grantees about nutrition research opportunities. The NCC's activities in reviewing interagency publications and documents can be found in the two sections that follow on collaborative interagency activities.

Definition of Nutrition Research at the NIH

The term *nutrition research* includes studies designed to assess the consequences of food or nutrient intake and utilization in the intact organism, including humans, and the metabolic and behavioral mechanisms involved. These studies encompass investigation of nutrient variables at the cellular or subcellular level. This definition also includes:

- **Research designed to elucidate the metabolic role or function of nutrients in both animal models and humans.**
- **All studies concerned with genetic-nutrient-environmental interactions where a nutrient is a variable.**
- **Dietary studies expected to produce significant changes in health status, including the maintenance of health and the treatment of disease in humans. Such studies might include clinical trials, epidemiological studies, metabolic studies, surveillance, and nutritional status monitoring studies.**

The NCC also sponsors conferences and workshops in nutrition; in FY 1990, there were 17 nutrition conferences and workshops, which are shown in appendix D. In addition, the NCC sponsors scientific seminars to coincide with its regular meetings. These special presentations on topics of current interest to NCC members are made by a variety of researchers and representatives of professional groups such as NIH grantees from the academic community, NIH investigators, and scientists from other Federal agencies. In FY 1990, the NCC sponsored six seminars; the abstracts are presented in appendix E.

The NCC liaison representatives offer a variety of assistance to the committee. The representative from the Warren Grant Magnuson Clinical Center provides information on research conducted in clinical nutrition and food service management (see section 2). The liaison representative from the Division of Computer Research and Technology designed and implemented the Human Nutrition Research Information Management (HNRIM) System, which is operated by the DNRC. The Division of Legislative Analysis staff member tracks information on proposed legislation affecting biomedical nutrition research and training (see section 2). The representative from the Division of Research Grants provides information on the number and types of nutrition-related applications submitted to the NIH and reviews new mechanisms and policies. From the National Library of Medicine, the staff member provides information on accessing scientific literature related to nutrition and other biomedical sciences. The representative from the Office of Communications assists the NCC by referring inquiries on nutrition-related topics from the media and public to appropriate NIH offices. The NCC also is assisted by its interagency liaison representatives from ADAMHA, CDC, FDA, HRSA, NCHS, ODPHP, and USDA.

NCC Nutrition Education Subcommittee - NES

Since 1978, the major responsibility of the NCC Nutrition Education Subcommittee has been to review nutrition education publications written for the public to assure institute-wide scientific accuracy and consistency in providing dietary guidance information (see appendix F for NES review procedures). The mandate of the NES also includes the following activities: identify mechanisms to improve nutrition education activities for professionals and the public; initiate, develop, or review nutrition activities or programs directed to NIH employees such as activities to commemorate Nutrition Month; and serve as advisors on nutrition issues, programs, or publications of other Government agencies when pertinent to the interests of the NIH and requested by the NCC.

NIH publications reviewed in FY 1990 by the NES included the NHLBI's *Check Your Weight* *and Heart Disease I.Q.* quiz, the revised version of NHLBI's *Facts About Blood Cholesterol*, NCI's *Eating Hints: Tips and Recipes for Better Nutrition During Cancer Treatment* and the NCC's *Nutrition Research at the NIH*. NIH nutrition publications for the public reviewed by the NES are included in the listing in appendix G.

The NES and the NCC were extensively involved in reviewing the third edition of *Nutrition and Your Health: Dietary Guidelines for Americans*, which was published in November 1990 (USDA/DHHS, Home and Garden Bulletin No. 232). The *Guidelines*, developed jointly by the U.S. Department of Agriculture and the Department of Health and Human Services, serve as the basis for all dietary guidance offered to the general population by agencies of the Federal government.

For the tenth consecutive year, activities to commemorate Nutrition Month were sponsored on the NIH campus in March by the NCC and NES, in cooperation with the GSI Cafeteria Service. The theme for the 1990 activities was *Reduce the Weight of Your World--Reduce Your Risk of Disease: Achieve Your Desirable Weight*. The cafeterias featured heart-healthy recipes from the "Play Your Cards Right...Stay Young at Heart" Program. Activities also included a series of seminars throughout the month of March on various aspects of obesity. Abstracts of these seminars are included in appendix E.

In FY 1990, the NIH-NCC Nutrition Research Exhibit was displayed and was well received at the annual meetings of the Federation of American Societies for Experimental Biology in Washington, DC, and the Society for Nutrition Education in Anaheim, California. The exhibit, developed by the NES, and its accompanying pamphlet, *Nutrition Research at the NIH*, serve to illustrate the NIH commitment to nutrition research; help to stimulate nutrition research related to the program interests of individual ICDs; and help to encourage high-quality applications for projects in the basic, clinical, epidemiological, and behavioral aspects of nutrition science.

Obesity Work Group

In FY 1990, the NCC established an Obesity Work Group which comprises representatives of the 11 institutes and centers at the NIH that support obesity-related research. The NCC Obesity Work Group sponsored a planning meeting with extramural scientists who are conducting research into various aspects of obesity on Biomedical Aspects of Obesity--Prevention and Treatment on August 3, 1990 (*NIH Guide for Grants and Contracts*, Vol. 20, No. 8, February 22, 1991).

The purposes of this preliminary meeting were to identify the major issues in obesity that should be addressed by the NIH, to make recommendations on activities to address these issues, and to prioritize topics and the mechanisms for NCC- and institute-sponsored activities to be initiated in 1991. The meeting discussions encompassed research questions, technology transfer activities, and public policy issues. Topics addressed included the current understanding of energy balance, issues in the prevention and treatment of obesity, special concerns regarding high-risk groups, risks associated with obesity, genetic and behavioral aspects of obesity, practices of weight loss programs, public awareness and information dissemination, and ways to stimulate basic and clinical obesity research. Activities recommended for NIH attention included investigating the clinical, molecular, and behavioral aspects of energy balance; working with other agencies towards providing the public with information on the prevention and treatment of obesity; targeting the prevention of obesity in childhood; improving understanding of special issues related to high-risk populations, such as women and certain ethnic groups; developing scientifically based weight standards, including considerations of age, gender, and ethnicity; increasing the emphasis on behavioral aspects of both energy intake and expenditure in obesity prevention and treatment; and applying the techniques of molecular genetics to an understanding of obesity. Currently, plans to pursue several of the recommended activities are in development by the Obesity Work Group.

Collaborative Interagency Activities at the DHHS Level

Nutrition Policy Board - NPB

Chair:	Deputy Assistant Secretary for Health, DPHP
Members:	NIH (DNRC), ACF, CDC, HRSA, FDA, ADAMHA, IHS, AOA

The NPB provides a forum to coordinate nutrition policy development and implement programs within the DHHS. The NPB facilitates the exchange of information on DHHS nutrition activities, provides advice and counsel to the Secretary of the DHHS on major nutrition policy issues, and serves as the focal point for nutrition policy matters with other Federal agencies as well as non-Federal agencies and organizations. The DNRC represents the NIH on the NPB; NIH liaison members of the NPB's Subcommittee on Dietary Guidance include the NCI and NHLBI.

NPB Subcommittee on Dietary Guidance

Chair:	Deputy Assistant Secretary for Health, DPHP
Members:	NIH (DNRC), FDA, ACF, AOA, HRSA, CDC, IHS
Liaison Members:	NIH (NCI, NHLBI), USDA (HNIS)

The NPB's Subcommittee on Dietary Guidance coordinates DHHS activities that offer dietary guidance information for healthy American populations. The subcommittee ensures departmental consistency with the principles established in the *Dietary Guidelines for Americans*; coordinates DHHS portions on dietary guidance; facilitates consistency of dietary guidance information from all Federal sources; and exchanges information on ways to improve the effectiveness of dietary guidance publications.

In FY 1990, members of the NPB and its subcommittee updated and reviewed the third edition of the *DHHS/USDA Dietary Guidelines for Americans*. The DNRC, NIH members of the NCC, the NES, and other NIH staff participated in reviewing this publication for the NIH. The revised guidelines were published in November, 1990.

DHHS Task Force on the Nutrition Objectives for the Nation

Lead Agencies:	NIH (DNRC), FDA
Members:	CDC, HRSA, IHS, NCHS ODPHP
Liaison Members:	APHA, ASTPHNPD, DOD, USDA

A decade ago, the Surgeon General published a broad list of health objectives that were to be achieved by 1990 for improved health status in priority areas related to health promotion and disease prevention. These objectives have been used as a basis for developing a new set of health objectives for the next decade. Nutrition continues to be a separate priority area of these objectives, reflecting the growing consensus about the important role nutrition plays in health promotion and disease prevention.

The Year 2000 objectives were prepared and released in the fall 1990 with the publication *Healthy People 2000: National Health Promotion and Disease Prevention Objectives* (DHHS Publication No. [PHS] 91-50212). The Year 2000 objectives expand and revise priority areas of the 1990 objectives, with additional focus on topics such as acquired immunodeficiency syndrome (AIDS), and increased attention to improvements in populations at high risk for premature death, disease, and disability. During FY 1990, the DNRC and several institute members of the NCC participated on the NIH Task Force on the Nutrition Priority Area Year 2000 Health

Objectives for the Nation and were extensively involved in writing and reviewing the nutrition priority objectives (see appendix B). The DNRC/NIH and FDA served as co-leads on the DHHS Task Force.

Collaborative Interagency Activities at the Federal Level

Interagency Committee on Human Nutrition Research - ICHNR

Chairs:	Assistant Secretary for Health, DHHS Assistant Secretary for Science and Education, USDA
Executive Secretariat:	NIH (DNRC)
Members:	DHHS (NIH, FDA), USDA (ARS, HNIS), NSF, AID, DVA, NASA, OSTP, DOD, DOC

The ICHNR was established to improve coordination and increase the effectiveness and productivity of Federal agencies engaged in nutrition research. The committee is concerned with all federally supported or conducted research on nutrition with emphasis on human nutrition and professional personnel needs in nutrition research. The committee also coordinates the collection, compilation, and dissemination of information on nutrition research, including the Human Nutrition Research Information Management (HNRIM) System. The DNRC represents NIH on the ICHNR and has served as executive secretariat to the ICHNR since 1986. The ICHNR has four subcommittees that carry out specific activities:

- Subcommittee on Research and the RDAs: identifies scientific issues that are of special relevance for the setting of dietary allowances.
- Subcommittee on Technology, Nutrition, and Food Production: monitors scientific, regulatory, and marketing developments with implications for the food supply.
- Subcommittee on Nutrition Monitoring Research: formulates an agenda of research tasks to improve capabilities in nutrition monitoring and interface with the Interagency Board on Nutrition Monitoring and Related Research.
- Subcommittee on the HNRIM System: reviews the classification system, codes, and contents of the data base.

In addition, the ICHNR organizes and sponsors the Biennial Conference for Federally Supported Human Nutrition Research Units and Centers. This meeting serves as a forum for information exchange and a stimulus for research collaboration among agencies. The fifth conference was held February 20-21, 1991, and addressed three topics of special interest to Federal nutrition researchers: "Studies on Dietary Risk Factors," "Minerals and Trace Elements--Requirements and Safe Levels for Humans," and "Energy Balance, Body Composition, and Obesity." Seventy papers were presented; a special *ad hoc* discussion on the Use, Cost, and Availability of Stable and Radioisotopes of Calcium for Research on Human Nutrition was held in conjunction with the meeting.

Fish Oil Test Materials Program - FOTMP

Fish Oil Test Materials Advisory Committee

Chairs:	NIH (DNRC), ADAMHA (NIAAA)
Members:	NIH (NCI, NHLBI, NIDDK), DOC (NMFS/NOAA), FDA (CFSAN), extramural scientists

This program was formally initiated in 1986 by the signing of a memorandum of understanding (MOU) among the NIH, ADAMHA, and the DOC/NOAA. Under the MOU, the agencies agreed to cooperate on and provide support to research activities related to establishing and clarifying the biological mechanisms by which a seafood diet or the ingestion of fish oils, including omega-3 (n-3) fatty acids, may influence health and modulate a number of human disease processes. The program is administered through the DNRC. The Fish Oil Test Materials Advisory Committee (FOTMAC) is advisory to the DOC.

The purpose of the FOTMP is to provide a consistent supply of quality-assured/quality-controlled test materials to researchers in order to encourage high-quality research and to facilitate the evaluation of the role that omega-3 fatty acids have in human health and disease. To fulfill this purpose, during the summer of 1987, NOAA completed construction of a pilot plant in Charleston, South Carolina, which is now producing fish oil test materials including n-3 ethyl ester concentrate, ethyl esters of olive oil, purified eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), encapsulated purified steam-deodorized menhaden oil with and without antioxidants, and antioxidant-balanced control oils (see appendix H for descriptions of the products). To qualify to receive these quality-controlled test materials, researchers must have a peer-reviewed research project indicating the need for the requested materials and submit a completed application form and a signed waiver of liability. Notices of the availability of fish oil test materials are periodically announced in the *NIH Guide for Grants and Contracts* (see appendix C).

Human Nutrition Research Information Management (HNRIM) System

Contributing Agencies:	DHHS (NIH, FDA, ADAMHA, HRSA, NCHS, CDC), USDA, DVA, AID, DOD, DOC, NASA, NSF

The HNRIM System is a unique computerized data base and data retrieval system that contains information on all nutrition research and research training supported by the Federal government. Now in its ninth year of operation, the system is updated and maintained by the DNRC, under the auspices of the ICHNR. Participating departments include DHHS, USDA, VA, AID, DOD, DOC, NASA, and NSF. The data base contains information on approximately 4,000 projects, with approximately 2,400 supported by NIH. The 17 ICDs at NIH that support nutrition research annually provide data for the system. For each research project, the following information is included: name, institution, and address of the principal investigator; sponsoring Federal agency; project number assigned by the agency; title; abstract, if available from the sponsoring agency; total fiscal year expenditures, proportion that is nutrition related, and estimated nutrition expenditures; and nutrition classification codes. Appendix I contains the nutrition classification codes used in the HNRIM System.

Computer readable copies of the HNRIM System data are available for purchase by the general public through the National Technical Information Service, DOC. The data base also is accessible to the public through Dialog Information Retrieval Service, as a subfile of USDA's CRIS data base.

Interagency Board on Nutrition Monitoring and Related Research - IBNMRR

Chairs:	Assistant Secretary for Health, DHHS Assistant Secretary for Food and Consumer Services, USDA
Members:	DHHS (NIH/DNRC, FDA, NCCDPHP, NCHS), USDA (HNIS, ARS, CSRS, FNS, FSIS, ERS), AID, DOC (Bureau of the Census, NMFS) Bureau of Labor Statistics, DOD, DVA, EPA

The IBNMRR was established in 1991 in response to the requirements of the National Nutrition Monitoring and Related Research Act of 1990, to serve as the Federal focus for the coordination, management, and direction of Federal nutrition monitoring activities. It is the successor to the Interagency Committee on

Nutrition Monitoring and oversees the effectiveness and productivity of nutrition monitoring efforts of the National Nutrition Monitoring System (NNMS), which includes all federally supported or conducted surveys on human nutrition and food consumption and surveillance of the food supply. The required activities of the IBNMRR include: reviewing progress on activities in the 10-year comprehensive plan on an annual basis as part of the budget and policy reports to Congress; providing for the review, evaluation, and revision of the 10-year comprehensive plan after 5 years of implementation; delivering biennial reports on policy issues to Congress; delivering periodic scientific reports that describe the nutritional and related health status of the population to Congress; and updating and publishing *Nutrition Monitoring in the United States: The Directory of Federal Nutrition Monitoring Activities* (DHHS Publication No. [PHS] 89-1255-1) every 3 years, including sources of non-Federal data.

To achieve its goals, the IBNMRR has three working groups:

- Survey Complementarity. This group aids the committee in working towards the integration of existing Federal surveys and surveillance activities into a network to provide a better overall view of both total population and special subgroups' nutritional health.
- Federal-State Relations and Information Dissemination and Exchange. This group assists the committee in improving information exchange between nutrition monitoring data users and data generators, with a special focus on federal and state relations.
- Food Composition Data. This group monitors the availability and quality of food composition data for use in the NNMS and identifies food composition data needed. It also proposes improvements to data to facilitate coordination among member agencies.

USDA/DHHS Nutrition Education Committee for Maternal and Child Nutrition Publications

Chairs:	DHHS (HRSA), USDA (FNS)
Members:	DHHS: NIH (DNRC), HRSA, IHS, ACF, NCEMCH USDA: FNS, HNIS, ES, NAL

This committee provides a systematic mechanism for the USDA and DHHS to exchange information on progress and plans related to efforts in maternal and child nutrition education. The committee reviews publications to assure consistency of content, stimulates greater collaboration on joint projects, and increases dissemination of information on nutrition education. The DNRC represents the NIH on this committee.

During FY 1990, committee members collaborated on several major activities which required the joint expertise of both departments:

- Development of *Nutrition Management of the Pregnant Adolescent: A Practical Reference Guide*
- Publication of *Quick & Easy: Commodity Recipes for the Food Distribution Program on Indian Reservations.*

For additional information on the DNRC and NIH NCC activities, contact:

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Section 2. Reports of Institutes, Centers, and Divisions

REPORTS OF PARTICIPATING INSTITUTES, CENTERS, AND DIVISIONS AND NIH LIAISON ORGANIZATIONS

Each of the 13 NIH institutes supports various aspects of nutrition research relevant to its particular research mission. Historically, the research and training focus of the institutes, centers, and divisions (ICDs) of the NIH has changed as technology has developed and as the science base needs of the research community have evolved. Together the research missions of the 13 institutes and 4 centers outlined here, as well as the activities represented by the NIH NCC liaison organizations, cover the disease conditions that are a major threat to the health and well-being of the American population.

Areas of scientific research do not readily lend themselves to sharp lines of demarcation. For this reason, the NIH program in biomedical and behavioral nutrition research and training is greater than the sum of the individual contributions of the NIH institutes, centers, and divisions that are described in this section. Ensuring and promoting this synergy is a vital task of the NCC. Thus, the individual descriptions of the nutrition activities and research directions that follow are not meant to be inclusive but rather to demonstrate the depth and breadth of the NIH's commitment to the field of nutrition. A list of the reports included in this section follows.

Institutes, Centers, and Divisions

National Cancer Institute
National Heart, Lung, and Blood Institute
National Institute of Dental Research
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute of Neurological Disorders and Stroke
National Institute of Allergy and Infectious Diseases
National Institute of General Medical Studies
National Institute of Child Health and Human Development
National Eye Institute
National Institute of Environmental Health Sciences
National Institute on Aging
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute on Deafness and Other Communication Disorders
National Center for Research Resources
John E. Fogarty International Center for Advanced Study in the Health Sciences
National Center for Nursing Research
National Center for Human Genome Research

NIH Liaison Organizations

Warren Grant Magnuson Clinical Center
Division of Legislative Analysis

Cancer is the second leading cause of death in the United States with more than 510,000 persons in 1990 dying from this disease. In the same period, more than 1,040,000 new cases of cancer occurred. Since the NCI was established in 1937, scientists have identified various cancer-causing factors in the environment, and research leaders have sought to reduce the exposure of the population to those risk elements. Research and training at NCI are carried out by both intramural and extramural programs of the Division of Cancer Prevention and Control, the Division of Cancer Treatment, the Division of Cancer Etiology, and the Division of Cancer Biology, Diagnosis, and Centers.

Since the establishment of the Cancer Prevention Research Program (CPRP) by the Division of Cancer Prevention and Control in 1982, a coherent cancer prevention research plan, focused on nutrition, has been developed. This program has both intramural and extramural components which, when interacting with other NCI divisions and programs, allow prevention strategies to flow efficiently from the laboratory to the clinic. The intramural components of the CPRP are the Cancer Prevention Studies Branch and the Laboratory of Nutritional and Molecular Regulation; the extramural components are the Chemoprevention Branch and the Diet and Cancer Branch.

NCI nutrition research is conducted with a variety of approaches: through epidemiologic studies of various population groups with distinctive food preparation and consumption patterns, by case-control and cohort studies, by clinical evaluations of dietary interventions, in laboratory studies of food content and components, and with biochemical/physiologic assessment of nutrient metabolism and absorption patterns in animals and humans.

RESEARCH DIRECTIONS

The NCI is giving substantial emphasis to nutrition in its programs to reduce mortality from cancer. The NCI supports extensive research on the relationship between nutrition and cancer in a wide variety of areas: prevention, epidemiology, etiology, basic cellular mechanisms, therapy, rehabilitation, research development, and information dissemination. Among the many research approaches being pursued, the following are of particular note:

- Through epidemiological investigations, assessments are being made about the effects of diet and nutritional status on cancer incidence and survival. Dietary factors under investigation include food groups, specific foods, cooking practices, and individual dietary constituents. Nutritional parameters under investigation include plasma cholesterol, serum fatty acid profiles, fecal bile acids, and serum micronutrient levels.
- Through chemoprevention and dietary clinical trials, studies are being carried out on the quantitative relationships between food, nutrient intake, and cancer incidence.
- Nutritive and nonnutritive dietary components are being assessed for their role in carcinogen metabolism.
- Investigators are studying mechanisms by which nutrients affect *in vitro* tumor cell metabolism and growth and the means by which chemotherapeutic agents alter cholesterol synthesis and cell membrane function.
- Methods of food preparation and processing, as well as ingestion of food and alcohol, fat, and fiber, are being appraised for their role in the promotion of cancer.
- Investigators are developing ways of measuring phytochemicals in fruits and vegetables and biological fluids and assessing phytochemicals for their potential role in cancer prevention.
- The correlation between levels of micronutrients associated with cancer risk in blood and tissues is being evaluated.
- The potential role of obesity, exercise, and immune dysfunction in cancer risk is

being explored through both epidemiologic and laboratory studies.
- Researchers are seeking nutritional agents that may serve in the chemoprevention of cancer and are developing methodologies to evaluate the cost-effectiveness of these prevention strategies.
- Accurate and reliable means of measuring human dietary intake are being developed.
- Improved methods for assessing nutritional status, metabolic patterns, and genetic predisposition are being evaluated for use in epidemiological studies.

Clinical aspects of the care and management of cancer patients require focused nutrition research, not on cancer prevention, but on the effective treatment of cancer. Among such investigative studies are the following:

- Clinical trials are underway to evaluate the effectiveness of nutritional support in the rehabilitation of the cancer patient, nutrition requirements during remission, and nutrient and dietary factors needed to maximize patient survival.
- The nutritional requirements of the cancer patient and neoplastic tissues are being appraised, with emphasis on nutrient uptake, utilization, and cellular control mechanisms in both normal and neoplastic tissues, and on host-tumor interactions and competition for nutrients.
- Knowledge of growth requirements and control mechanisms helps to formulate new therapy schemes based on differential nutrient availability.
- In order to develop techniques and procedures to maintain or improve the nutritional status of the patient, various formulations and delivery systems in total parenteral and enteral nutrition and oral supplementation are being examined. Energy expenditures also are being measured using whole body calorimetry. Behavior modification procedures and pharmacological agents are used to improve the appetite of cancer patients. In addition, laboratory research is underway on the etiology of cachexia, or wasting, in cancer patients.
- Educational materials and programs are being developed on the role of diet and nutrition in cancer etiology, prevention, treatment, and rehabilitation for dissemination to health care professionals and to the public.
- Investigators are studying mechanisms by which nutrients affect tumor cell metabolism and growth, including the accumulation of intracellular metabolites and alterations in glucose production in cancer cachexia; the effect of total parenteral nutrition on tumor growth and polyamine metabolism; the nutritional effects of nucleotides on lymphocyte function; and regulation of glutamine metabolism through high glutamine diets and tumor metabolism.
- A clinical study is underway to examine the effect of megestrol acetate on weight gain in stage III non-small cell lung cancer patients. Three possible mechanisms will be studied: increased food intake, decreased energy expenditure, and fluid retention.
- Clinical trials are underway to evaluate the effectiveness of low-fat dietary patterns in preventing the recurrence of breast cancer, skin cancer, and adenomous polyps.
- The cooperative groups are studying the effects of therapeutic interventions affecting nutrition in several randomized trials.

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The diseases within the purview of the NHLBI impose a heavy burden on the health and economy of the American people. Cardiovascular, lung, and blood diseases accounted for 1,159,000 deaths in 1987 or 54 percent of all deaths. They represent 5 of the 10 leading causes of death, 6 of the 10 leading causes of infant death, and 5 of the 13 leading chronic conditions that result in varying degrees of limitations of activity. Cardiovascular diseases alone were responsible for approximately 46 percent of all deaths in 1987.

The NHLBI provides leadership for a national program in diseases of the heart, blood vessels, lungs, and blood, and in the uses of blood and management of blood resources. Through its intramural and extramural programs, the NHLBI conducts and supports an integrated research program that includes basic research, clinical trials, epidemiologic, and demonstration and education projects that relate to the causes, diagnosis, treatment, and prevention of heart, blood vessel, lung, and blood diseases. In addition, the NHLBI supports research training of new investigators and the career development of established researchers in both basic and clinical research related to heart, blood vessel, lung, and blood diseases and transfusion medicine.

The institute's overall objective in integrating basic and clinical research and disseminating information about health care strategies is to reduce the morbidity and mortality of heart, lung, and blood diseases in the United States. The NHLBI's research and training program is administered through a variety of funding mechanisms. In its nutrition program as in other NHLBI research, the institute's research efforts are focused in four extramural divisions: the Division of Heart and Vascular Diseases, the Division of Lung Diseases, the Division of Blood Diseases and Resources, and the Division of Epidemiology and Clinical Applications. Additional studies are conducted in the Intramural Division.

The Office of Prevention, Education and Control (OPEC) is responsible for the development and dissemination of nutrition information and materials related to the risk factors for cardiovascular heart disease. Much of this information, disseminated to health professionals, patients, and the public, is based on program activities of the National Cholesterol Education Program (NCEP), National High Blood Pressure Education Program (NHBPEP), and the new NHLBI Obesity Education Initiative. The Obesity Education Initiative was initiated in early 1991 in order to enhance and integrate obesity education activities underway by the NCEP, NHBPEP, and the NHLBI Smoking Education Program. Other OPEC programs underway include the National Asthma Education Program and the National Blood Resource Education Program. All of these programs and initiatives are designed to provide the most recent scientific information about heart, blood vessel, lung, and blood diseases to health care practitioners, patients, and the public.

RESEARCH DIRECTIONS

In its nutrition program, as in other NHLBI research, the institute's prevention efforts are targeted toward heart and vascular diseases, lung diseases, and blood diseases and resources. The following are examples of research supported by the NHLBI:

Heart and Vascular Diseases

- Identify mechanisms by which nutrients and other dietary factors influence blood pressure both under normal conditions and with hypertension.
- Explore the role of nutrition in intervention studies of cardiovascular disease risk.
- Conduct studies to determine the basis for racial, ethnic, and gender differences in CHD rates, including metabolism, risk factors, and diet responsiveness.
- Identify behavioral determinants of food consumption patterns and nutrient intake in relation to the risk of disease and the promotion of health.
- Improve the measurement of diet and nutrient intake, including acquisition of food composition data and development of

automated methods of assessing dietary intake of individuals.
- Develop effective nutrition education strategies, methods, and materials for the dissemination of information on nutrition and disease prevention to health professionals and to the public in schools, worksites, clinics, and communities.
- Support training in nutrition as it relates to heart and vascular diseases.
- Elucidate the role of body weight and diet in cardiovascular disease and its risk factors.
- Continue surveillance of public knowledge and physician practices that pertain to diet and cardiovascular disease.

Lung Diseases

- Improve the understanding of the effects of nutritional status on immune defense functions in the developing and adult lung; the effects of malnutrition on normal resistance to pulmonary infections; and the role of nutritional factors in the development of bronchopulmonary dysplasia.
- Explore the role of nutrition in preventing respiratory muscle dysfunction in acute and chronic pulmonary disease.
- Support studies on the role of various nutrients on nonrespiratory lung functions, such as the synthesis and metabolism of surfactant and prostaglandins.
- Determine the effect of dietary factors on the central control of breathing and on neurophysiology within the lung and airway tissues.
- Investigate the role of specific nutrients in adult and infant respiratory distress syndromes and in other forms of respiratory failure.
- Support training in nutrition as it relates to lung diseases.

Blood Diseases and Resources

- Identify mechanism(s) by which nutrients and other dietary factors influence the blood-clotting function of platelets.
- Elucidate the role of nutrients and other dietary factors in the genesis, treatment, and prevention of blood vessel obstruction.
- Continue research on energy balance and nutrient requirements among children with sickle cell disease, especially children who fail to thrive and adolescents who are in the rapid growth phase.
- Determine the time of appearance and the intensity of nutritional abnormalities in sickle cell patients.
- Conduct studies on the benefits of appropriate dietary intervention and nutritional supplementation on growth and development and on the morbidity of children with sickle cell disease.
- Improve understanding of nutritional factors in the management and clinical variability of sickle cell anemia.
- Characterize the relationship of nutritional deficiencies and immune dysfunction in sickle cell disease.
- Support training in nutrition as it relates to blood diseases and resources.
- Elucidate the role of nutrients and other dietary factors on the genesis and treatment of high blood pressure.
- Support research in nutrition education for medical students and for physicians in their private practice.
- Continue to support research to improve assessment and control of diet in research studies.

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The NIDR is the primary sponsor of oral health research and related training in the United States. Its mission is to support studies to establish the causes, to develop better treatments, and to find ways to prevent or substantially lower the risk of developing oral diseases and disorders.

Institute scientists, as well as those affiliated with grant-supported NIDR programs, have made encouraging progress in improving the nation's oral health through advances in diagnosis, treatment, and prevention. The institute has organized its efforts into an Extramural Program (EP) and the Intramural Research Program (IRP) centered in NIDR's own laboratories and clinics in Bethesda. The NIDR added an Epidemiology and Oral Disease Prevention Program to the IRP in the mid-1980s. This program sponsors epidemiologic studies of oral diseases and disorders and engages in demonstration research and controlled clinical trials of potential preventive agents and regimens, promoting their dissemination to the dental profession and the general public.

The NIDR "Research and Action Program for Improving the Oral Health of Older Americans and Other Adults at High Risk" aims to prevent tooth loss and further deterioration in oral health status among older Americans. The Research and Action Program also is designed to spur the basic and clinical research necessary to drive nationwide public and private sector actions to improve the oral health of all Americans, as well as to facilitate and encourage other organizations to expand their own activities.

The NIDR's new Long-Range Research Plan for the Nineties, *Broadening the Scope*, reflects the major growth of oral health research and a commitment to address all the diseases and disorders that affect the orofacial tissues. Thus, in the special section on nutrition there are recommendations for research on the effects of dietary factors on specific diseases, including caries, periodontal diseases, diabetes, osteoporosis, and oral cancer, in addition to research on nutrition in relation to the normal growth and development of the oral tissues.

In addition to the Research and Action Program, a second initiative in the NIDR Long-Range Research Plan for the Nineties focuses on individuals whose oral health is compromised because of medical conditions (and their treatments) or because of physical or mental handicaps. The plan also calls for increased research on ways to improve the oral health of racial and ethnic minorities.

RESEARCH DIRECTIONS

NIDR's nutrition research focuses on the relationship between diet and the development and maintenance of both hard and soft tissues of the oral-facial complex. Special interests are in the areas of tooth and gum development and maintenance, periodontal diseases, and dental caries, particularly as they are affected by nutritional factors. Examples of nutrition research supported by the NIDR include:

- Studies on the effects of nutrients during embryonic life, particularly as they relate to oral structures, (e.g., the role of nutrition in craniofacial malformations and developmental defects of cleft lip and palate).
- Investigations to determine the effects of poor nutrition on the fundamental integrity and metabolism of oral soft tissues, (e.g., the effect of nutrition on salivary gland function, including the secretory immune mechanism).
- Research on the effects of nutrition on the biology of bone and soft tissue, the etiology and prevention of oral ulcerative diseases, and immune function.
- Research to define critical periods of development of oral tissues that may be sensitive to nutrient intake and the role of nutritional factors in the maintenance and repair of the periodontium and other oral tissues.
- Research on the role of nutrition and nutritional status in the etiology and pathogenesis of oral diseases in older persons and other high-risk populations.

- Research to define mechanisms underlying relationships between oral diseases or conditions and chemosensory disorders.
- Examination of the metabolic effects of various fluoride levels in humans, especially the effect of fluoride received prenatally, and investigation of dental fluorosis.
- Studies on the effects of zinc deficiency on the epithelium lining in some regions of the oral cavity.
- Investigation into the structure, nutritional requirements, and normal functioning of salivary components, such as mucins (important in lubrication), histidine-rich proteins (with specific antifungal properties), and proline-rich proteins (important in remineralization of tooth enamel).
- Research on the effect of dietary factors, such as alcohol, on the initiation and progression of oral cancers and the role of vitamin E- and vitamin A-related compounds in the control or reversal of cancerous lesions.
- Research on the role of nutrition in wound healing.
- Research on the molecular basis of taste and in the development of safe, noncaloric sweeteners that are also noncariogenic.
- Research to assess fluoride bioavailability and incorporation into hard and soft tissues, and the safety and disease-preventing efficacy of fluorides in various fluoride-containing vehicles.
- Research on safe, short-term intraoral methods to assess the caries-producing potential of foods and the effectiveness of anticariogenic agents.

OUTLOOK

The NIDR Long-Range Research Plan for the Nineties, *Broadening the Scope,* emphasizes the need to expand research to include all the diseases affecting the teeth, the mouth, the face, and the jaws. The institute's nutrition research is an important component in this effort, concerned with the effects of diet and nutrients on the development, maintenance, and repair of the orofacial tissues and in the prevention of disease. Special emphasis is placed on the role of eating habits and nutrition in relation to the oral and general health of ethnic and racial minorities, women, older Americans, and medically compromised patients, including studies of ways to change behavior to favor the adoption of healthy diets.

For more information on the NIDR nutrition program, contact:

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NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Since its creation in 1950, the NIDDK's research responsibilities have included nutrition-related programs to prevent and treat disorders such as liver and biliary diseases; pancreatic diseases; gastrointestinal, digestion, and absorption disorders; diabetes; obesity; a variety of endocrine disorders; kidney and urological diseases; metabolic diseases, including cystic fibrosis; and eating disorders. The NIDDK plays an important role in the study of nutritional factors relating to the etiology, prevention, and treatment of diabetes, digestive, and kidney diseases. This research is supported out of three divisions: the Division of Diabetes, Endocrinology, and Metabolic Diseases; the Division of Digestive Diseases and Nutrition; and the Division of Kidney, Urologic, and Hematologic Diseases.

More recently, an expansion of nutrition research training in the areas of nutrient metabolism, obesity, eating disorders, and energy regulation is being encouraged. In response to the fact that both applications and awards in research training have declined since the beginning of this decade, an annual request for applications (institutional training grants, individual postdoctoral fellowships, and career awards) has been initiated as a means to re-establish a strong nutrition research training base in the 1990s.

The NIDDK has created a National Task Force on Prevention and Treatment of Obesity. This Task Force will help synthesize current, scientifically based information about obesity through the development of summary documents on a series of important issues related to its prevention and treatment. The task force also will help identify concepts for possible future clinical research studies in obesity. The overall goal of the NIDDK is to effect the transfer of information underpinned by a strong scientific foundation to benefit the American public in the prevention and treatment of obesity.

RESEARCH DIRECTIONS

The NIDDK fosters and supports other nutrition research and training, especially in the following broad areas of fundamental and clinical nutrition:

- Research on dietary requirements (and safe levels) of many nutrients needed for health maintenance, proper growth and development, and a state of well-being at all ages and under various conditions, such as stress, drug use, nutrient imbalances, and changing activity levels.
- Fundamental studies exploring nutritional factors that are active in absorption and metabolism, the biological control of such processes, and the identification of unrecognized roles of nutrients or their metabolites.
- Assessment of the impact of omega-3 fatty acids on prostaglandin biosynthesis and metabolism, their influence on membrane function, and their potential role in the development and progression of disease processes.
- Research on fiber to determine its chemical characteristics in order to determine its effects on intestinal microflora and food transit time; its interaction with nutrients, bile acids, and other substances in the gut; its effects on digestive enzymes and absorption; and the development of improved routine methods for analyzing its components.
- Assessment of the requirement levels and metabolic roles of trace elements, with the help of reliable, newly developed, analytical methods.
- Research on relationships between genetic predisposition, induced metabolic changes, thermogenesis, environmental and physiological factors, and lifestyles that result in greater energy intake than expenditure (for obesity prevention and control).
- Development of methods for characterization of various types of obesity and determination of the health consequences of repeated cycles of weight gain and loss.
- Investigation of how chronic feeding of diets high in fat and glucose increases blood pressure and enhances sympathetic nervous system activity in rats.

- Studies of the mechanism and efficacy of pharmacologic agents on energy balance and weight control.
- Investigations on how dietary polyunsaturated fats uniquely regulate fatty acid synthesis.
- Determination of the most effective individual, group, and community intervention strategies for weight management.
- Investigation into the contribution of genetic and metabolic factors to obesity causation, including the molecular and genetic basis of energy metabolism and the nature of genetic aberrations in human obesity.
- Research to improve nutritional support to hospitalized patients, to improve nutritional status assessment methodology, and to acquire more information about the effects of disease states on the nutritional needs of patients.
- Investigation of dietary modifications that may retard the rate of progression of endstage renal disease, reduce the need for dialysis, or both.
- Investigation of the mechanisms by which nutrients might affect renal function.
- Studies of the causes of wasting malnutrition and other nutritional disorders that occur in renal failure.
- Research on the interplay of dietary factors (such as calcium, vitamin D, phosphate, protein, and oxalate) in the etiology of renal stones.
- Studies on hormones that regulate bone metabolism, nutrition and nutrient metabolism and the maintenance of calcium balance, especially as related to osteoporosis and related bone disorders.
- Studies to elucidate the endocrine and metabolic basis of wasting in AIDS.
- Research on the role of cachectin and/or other monokines in the pathogenesis of wasting in AIDS and other chronic diseases.
- Studies on the role of calorie intake and physical activity, and subsequent weight control, in the prevention of type II diabetes.
- Investigation of the metabolic mechanisms of intestinal and hepatic processing of dietary carbohydrate and the effects of other nutrients and of fiber on carbohydrate metabolism.
- Clinical research into nutrition-related areas such as cholesterol and pigment gallstones; inborn errors in bile acid metabolism; chronic hepatitis that evolves from autoimmune, viral, or alcoholic disease; and various liver diseases, such as Wilson's disease and portal hypertension.
- Investigations into the control of appetite, satiety, and anorexia in normal individuals, as well as in those with various disease states.
- Exploration of mechanisms for the development of gastrointestinal malabsorption in AIDS patients and investigations of other metabolic perturbations of nutrient metabolism, such as lipogenesis, to develop rational means of nutritional support of these patients.
- Funding of five Clinical Nutrition Research Units and the Obesity Core Center, each conducting an intensive program of nutrition research.
- Identification of hormones, growth factors, lipid mobilizing factors, or other peptides that may contribute to wasting in AIDS.
- Regulation of muscle mass and nitrogen balance in AIDS.
- Studies of whether abnormalities in insulin secretion or sensitivity may be involved in decreased fat stores in AIDS.

For more information on the NIDDK nutrition program, contact:

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NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

Created in 1950, the NINDS supports and conducts research and research training on the brain and the nervous system, and neurological and neuromuscular disorders. Among the diseases and disorders being studied are brain and spinal cord trauma, Parkinson's disease, Huntington's disease, Alzheimer's disease, epilepsy, stroke, brain tumors, neuro-AIDS, multiple sclerosis, muscular dystrophy, Batten's disease, Gaucher's disease, amyotrophic lateral sclerosis, and sleep disorders.

In 1989 President Bush signed into law a House Joint Resolution that declared the 1990s the "Decade of the Brain," calling upon the Nation to observe the decade with appropriate activities. Recent years have witnessed tremendous progress and exciting achievements in brain and nervous system research. Through these discoveries, the NINDS has identified numerous compelling neurological disease areas and research issues for which opportunities exist to make extraordinary advances in the nineties.

RESEARCH DIRECTIONS

As more is learned about the brain, the extent of the interaction between nutrition and the nervous system is evolving and rapidly changing; however, many issues are still controversial and inconclusive. The NINDS nutrition research program continues to support studies to clarify the relationship between nutrient intake and the central nervous system and, conversely, the influence of the brain upon dietary patterns and its role in the etiology of obesity and eating disorders. The efficacy of nutritional interventions to prevent and treat various neurological disorders is also under investigation.

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NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Although the NIAID was established in 1948, it traces its roots back to the Laboratory of Hygiene, a bacteriological laboratory that was founded in 1887 and was the forerunner of the NIH and the NIAID. The NIAID supports basic and clinical research in microbiology, infectious diseases, immunology, and allergy. A major component of NIAID's basic research is concerned with fundamental life processes as exemplified in microorganisms and in animal cells *in vitro*. Techniques and basic biologic principles, developed as a result of this fundamental research in microbiology and immunology, have then been applied to the other areas of biology and medicine, including nutrition.

The complex interrelationships among nutrition, microbial infections, and immunology have important health implications. In the developing world, more than 1 billion cases of infectious diarrheal disease occur yearly in children under the age of 5 years. Malnutrition both predisposes to diarrhea and occurs as a result of diarrhea. Immunodeficiency states, such as AIDS, cause malnutrition and set the stage for superinfections that accelerate the cycle of malnutrition and infection. Asthma and allergic diseases affect over 40 million Americans. Surgery and trauma lay the groundwork for infection and subsequent malnutrition. Many of these infections and conditions, or their complications, can be mitigated, at least in part, by appropriate nutrition.

NIAID's studies on nutrition are an integral part of the institute's research to lessen the adverse health consequences of immunologic and infectious diseases. Of particular significance are the consequences of wasting on the underlying AIDS disease process, its infectious and immunological complications, and the role of nutrition in the development of safe and effective vaccines against infectious diseases.

Continuing concerns are the prevalence of infections among the malnourished, the effect of infections on nutritional status, the prevalence of food-borne microbial illness and its control, and the effect of malnutrition on resistance to infection, especially to infectious diarrhea in young children.

RESEARCH DIRECTIONS

NIAID's interest in nutrition aims at a better understanding of the complex interrelationships of nutrition, immunity, and infection. The institute's research directions are correspondingly varied. They include the following:

- All aspects of nutrition and the development and consequences of AIDS.
- The negative effect of malnutrition on resistance to tropical infections (especially infectious diarrheas) and the role of breast milk as a defense against enteric infections.
- The significant morbidity and mortality of rotavirus-induced infectious diarrhea among infants in developing countries and a major effort to develop a safe, effective, and practical rotavirus vaccine for newborns.
- The role of minerals, especially iron, on the metabolism and virulence of bacteria and fungi.
- The role of nutritional factors in the immune response to animal parasites that cause significant human disease, e.g., schistosomiasis, giardiasis, and cryptosporidiosis.
- Infections in American hospitals, including the effect of surgery on immune function, hypercatabolism, and resistance to infection.
- The modulating effects of specific nutrients (e.g., vitamins, trace elements, fatty acids, fiber, and amino acids) on basic immune function.

- The relationship of specific foods to allergic reactions such as anaphylaxis and eczema, the immune response to ingested antigens, including milk, soy, and egg, and the role of foods in immunologically mediated gastrointestinal diseases, such as sprue and inflammatory bowel disease.

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NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

The principal mission of the NIGMS is to support fundamental research that undergirds all biomedical investigations. The major focus of the institute is on research concerned with expanding knowledge of fundamental biological structure and function at the cellular and molecular level. Extramural studies supported by the institute include investigations in the biophysical sciences and the physiological sciences, in particular; the response of the whole body to trauma, the structure and function of the cell, the basic mechanisms of heredity, and the molecular aspects of the interactions between therapeutic drugs and agents and their target cells, tissues, or organs.

The great majority of the nutrition-related research supported by NIGMS is in its trauma and burn injury program area, which focuses on the mechanisms involved in the body's systemic responses to trauma. Thus, research on the role of nutrition in decreasing morbidity rates for patients who suffer serious trauma or burn injury is of significant interest to the institute. NIGMS-supported scientists are exploring nutritional requirements following severe trauma and sepsis, new concepts in parenteral therapy, branched chain amino acid feeding during injury, and cellular function during septic and hemorrhagic shock. In addition, there are studies being supported that are investigating the cellular changes and mechanisms responsible for the protein wasting associated with nutritional deprivation.

RESEARCH DIRECTIONS

The following leads are being pursued that pertain to basic research on diseases and also traumatic injury:

- The role of diet in organ and cellular responses to cytokines.
- Change of metabolic patterns and nutritional requirements following severe injury.
- Hormonal imbalance following injury and its effects on metabolism.
- Mechanisms involved in producing a protein catabolic state after injury.
- Adaptive regulation of nutrient transport by the gut. Transport appears to be governed by nutrient-receptor proteins on specific cell surfaces.
- Mechanism of suppression of lipoprotein lipase activity by TNF. Pools of mRNA which code for the lipase are perhaps depleted in the presence of TNF.
- Which components of the host defense system (neutrophils, immunomodulators, etc.) are important in preventing bacterial translocation.
- Receptors that recognize serum proteins carrying galactosyl sugar residues, including hormones that regulate the rate and extent of nutrient uptake and processing in the liver.
- The importance of enteral versus parenteral feeding.
- The inclusion of glutamine and human growth hormone in nutritional regimes.

OUTLOOK

Research supported by the NIGMS serves to establish the foundation of new knowledge needed to make advances in the understanding of many diseases. Those investigations that are nutrition-related will help to provide the concepts and relevant information necessary to develop new treatments, particularly in the area of traumatic injury, and hence, serve to decrease morbidity and mortality.

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NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Since the NICHD was created in 1963, its nutrition research program has focused on the continuum of human development, from conception through infancy, childhood, and adolescence. The program emphasizes preventive approaches to nutrition-related conditions and stresses health promotion as well as disease prevention. Much of the research is multidisciplinary in nature and involves the genetic, biochemical, developmental, anthropometric, behavioral, and cultural aspects of nutrition. The NICHD supports research on maternal and fetal nutrition; nutrition during infancy, childhood, and adolescence; the relationship of nutrition to reproduction; behavioral and cultural aspects of nutrition; obesity and its nutritional antecedents; nutritional therapy of inborn errors of metabolism; and assessment of nutritional status.

The institute has a strong interest in the nutrient requirements of normal, premature, and low birth weight infants, as well as in the composition of human milk, cow milk, and synthetic formulas, in relation to optimal infant nutrition. In some of this work, the interest centers on metabolic processes in neonatal adaptation and on the role played by essential nutrients and other components of human milk. Research on cultural and behavioral determinants of nutritional individuality includes studies of habits, taste, and olfaction; food avoidances; and behavior modification of dietary intakes. Research on nutritional antecedents of adult disease focuses primarily on factors in the development of obesity in infancy, childhood, and adolescence.

The NICHD has completed work with a group of consultants on the development of a new institute Five Year Plan for Nutrition Research and Training. The aims of the plan are as follows:

- To identify the global issues in maternal-fetal, neonatal, infantile, childhood, and adolescent nutrition.
- To pose key questions about these global issues, including epidemiologic questions.
- To identify the technology needed to address these key questions.

The plan is expected to have an important influence on the activities supported by the NICHD, providing information needed for the development of areas of emphasis and the allocation of resources for nutrition research within the institute's programs. Subjects identified for attention in the new Nutrition Research Plan are nutritional epidemiology and international nutrition, trace elements and micronutrients, nutritional therapy of inborn errors of metabolism, obesity and energy metabolism, feeding of low birth weight and term infants by enteral and parenteral nutrition, lipoproteins and antecedents of adult vascular disease, nutritional influences on gastrointestinal development, maternal-fetal nutrition, fetal growth factors, nutrition and brain development, and human milk research. It is expected that the new plan will be published in FY 1991.

RESEARCH DIRECTIONS

A few examples of current nutrition research supported by the NICHD are as follows:

- Studies on the effects of vitamins on reproductive function and morphology and on the relationship between oral contraceptive use, cervical dysplasia, and folate levels.
- Maternal-fetal nutrition research on the mechanisms of placental transfer of essential nutrients and the influence of these nutrients on normal and abnormal fetal development.
- Studies of events governing development of the gastrointestinal tract from fetal life to adulthood. The role of human colostrum and milk in stimulating development of the gastrointestinal tract and protecting it from disease are of special interest.

- Studies of human milk, cow milk, and synthetic formula to assess the requirements for optimal growth and development in normal and low birth weight infants.
- Research on the nutritional antecedents of various adult diseases, including the nutritional ramifications of diabetes in pregnancy for infants born to diabetic mothers; the development of obesity in infancy, childhood, adolescence, and early adulthood; and dietary, genetic, and metabolic precursors of atherosclerosis.
- Studies of behavioral, neurochemical, genetic, and hormonal factors in childhood obesity.
- Studies of the influence of nutritional factors on cognitive development and behavior in both normal subjects and patients with inborn errors of metabolism.

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The National Eye Institute (NEI) has for the past 22 years dedicated itself to reducing the prevalence of blindness, visual impairment, and eye disease in the United States and throughout the world. The Office of International Program Activities is the focus of the institute's international nutrition-related activities, including those to understand, alleviate, and prevent nutrition-related blindness.

As much as 80 percent of the 40 million cases of blindness worldwide are considered curable or preventable. Xerophthalmia, a potentially blinding disease caused by vitamin A deficiency, is the leading cause of nutrition-related blindness and visual impairment among the world's children. It accounts for 70 percent of the estimated 1.5 million blind children in the world. Mild vitamin A deficiency with consequences for child health and survival affects another 20 to 40 million children worldwide.

The NEI supports research on the role of general nutrition and on specific nutrients such as vitamins A, C, B_6, and E, as well as protein, copper, and zinc on normal ocular and visual development, health, and function. Scientists supported by the NEI also are examining the association between nutritional imbalances and eye and vision disorders, such as cataract, retrolental fibroplasia, retinitis pigmentosa, gyrate atrophy, macular degeneration, and other visual disabilities.

RESEARCH DIRECTIONS

The following projects represent many of the nutrition-related research areas supported by the NEI:

- Investigations into vitamin A, its derivatives, and the proteins that bind it to cells and transport it between and within cells are a major focus of NEI-supported investigations. Scientists are exploring the role these substances play in the normal metabolism of ocular tissues and in the visual process. Alterations of ocular tissue integrity and of its metabolism brought about by chronic deficiency of vitamin A also are being studied. These investigations include studying the role of vitamin A in maintaining the immune competence of the eye and the ability of ocular tissues to respond to infections and trauma.
- Operations research studies related to prevention of vitamin A malnutrition, which is the major cause of preventable blindness among children in the developing world, are underway. Scientists are conducting epidemiological studies to identify the nutritional and environmental factors that act with vitamin A deficiency to increase the risk of mortality from infections and of developing xerophthalmia and the irreversible corneal damage and destruction caused by keratomalacia. Methods for assessing the relative vitamin A status of individuals also are being evaluated.
- NEI-supported scientists are using dietary assessment interviews to determine the intake of 17 major nutrients and alcohol in a community of 4,800 older adults. Blood samples are being analyzed to measure levels of potentially important nutrients for which dietary estimates are difficult to obtain or for which there are inadequate measures to evaluate their nutrient status.
- Investigators are studying the cloning and sequence analysis of the human gene responsible for encoding the cellular retinaldehyde-binding protein from retina. Because of the possible involvement of this gene in hereditary retinal diseases such as retinitis pigmentosa, scientists are attempting to confirm the cellular localization of this protein by *in situ* techniques and to determine the chromosomal location of the human gene. Scientists believe that the combined results from this research will provide a precise molecular framework in which questions concerning the normal function of this protein and the visual disorders it may be associated with can be answered in specific terms.

- Scientists are studying the mucosal immunity of the eye, particularly the response and function of the rat ocular secretory immune system, with emphasis on the impact of aging and nutrition on immunological activity in the eye. These investigations address the functional role of the secretory immune system, which serves as the first line of defense to protect the ocular surface against bacterial colonization and viral invasion.
- Scientists are studying the roles of vitamins E and C in nourishing ocular tissues and in maintaining visual acuity during natural and induced chronic and acute exposure to oxidants.
- The NEI also supports research on cataract and macular degeneration, both of which are major causes of visual disability and blindness. The nutrient environment in which cataract and macular degeneration develop and the potential for altering this environment to prevent or arrest the cataractous and degenerative processes are additional foci of research activity. Deficits of antioxidant nutrients are under particular scrutiny in studies to clarify the etiology of cataract.
- Research is ongoing on the fundamental role played by essential minerals, such as zinc, calcium, and magnesium in lens metabolism and on the consequences for eye health of disturbances in mineral balances. The association between ascorbic acid levels in ocular fluids and the healing process after corneal trauma is also under investigation.
- Several studies are underway to detail the function of essential minerals that play a critical role in retinal function and in intraocular transport and function. The NEI also supports studies to determine whether dietary modifications may be effective in correcting the biochemical abnormalities associated with gyrate atrophy and other retinal degenerative diseases.

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NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

In 1966, the Secretary of the Department of Health, Education and Welfare established the Division of Environmental Health Sciences as a part of the NIH. The division was elevated to institute status in 1969. To attack environmentally related health problems, the NIEHS supports a broad spectrum of biomedical research ranging from basic studies at the cellular and molecular levels to more applied programs aimed at identifying hazardous environmental substances and understanding both the effects from exposure to them and the mechanism by which they may cause biological damage. The institute, which has its headquarters in Research Triangle Park, North Carolina, performs research in its intramural laboratories and through sponsored research throughout the United States and the world.

During the past year, the American public's concern over chemical contamination of our food and water supply has been at an all time high. Around the breakfast table, news headlines have included stories on pesticide residues in food supplies, contaminated drinking water, and cancer in fish.

Determining the identity and nature of these and other chemical, physical, and biological factors in the environment that may affect human health is at the core of NIEHS research. It also is reflected in the commitment of the institute to the National Toxicology Program (NTP), a DHHS interagency effort that attempts to fill information gaps about the possible toxicological effects of human exposure to environmental chemicals. Institute grantees and intramural scientists have utilized this extensive data base of scientific knowledge to facilitate their own research.

RESEARCH DIRECTIONS

NIEHS is exploring a number of areas that hold promise for furthering our understanding of the relationship between nutritional factors and human health. Selected examples include:

- In July 1990, the institute held a meeting to address a broad range of concerns that arise from the potential impacts on human health of the great volumes of chemicals used in agriculture, many of which become a part of the food sources.
- Cow's milk contains a number of kinins--a family of polypeptides that act in the contraction of smooth muscle. Recent findings from an NIEHS study have found several kinins including bradykinin in milk which has provided chemical evidence regarding the likely involvement of these compounds in postnatal development. The long-term goals of this project include identifying the physiological significance of these molecules.
- It is well known that dietary restriction reduces spontaneous tumor incidence in animals. A study is under way to explore this relationship further to see if the incidence of chemically induced tumors can be reduced by limiting caloric intake.
- In order to establish/minimize the health risks resulting from exposure to hazardous substances, regulatory bodies require scientific data. A new project is underway that examines environmental substances that are potentially carcinogenic and are food-borne toxicants. The program will focus on carcinogens to which intermittent human exposure at low levels is virtually unavoidable and that have been established as risk factors for human cancers by epidemiologic studies.
- Monitoring and controlling for the presence in grain and food products of aflatoxin, a potent liver carcinogen, is hampered by difficulties in applying sophisticated analytical chemistry techniques in field settings. Through its small business program, NIEHS has developed sensitive devices for measuring this contaminant in the field.
- An NIEHS study has identified a number of mutagens formed when beef is fried or broiled under normal household cooking conditions and determined the effects of time and cooking temperature on mutagen formation. Studies continue to identify additional mutagens, cooking methods to prevent mutagen formation, and biomarkers of exposure to these mutagens.

- A number of studies examining breast milk as a source of chemical exposure are planned or underway. In Mexico, an NIEHS study is looking at the duration of lactation and illness of children exposed through mother's milk to DDE, a metabolite of DDT. An animal model is being developed for the study of offspring exposure to drugs and other chemicals through mother's milk. In the course of this work, the drug cimetidine has been found in the milk of rats in concentrations 25 times higher than in plasma. The mechanism of concentration is still under investigation.
- The Clean Air Act of 1990 requires NIEHS to conduct a study to determine the threshold level of mercury exposure below which adverse human health effects are not expected to occur. This study will include a threshold level for mercury concentrations in fish which may be consumed, including consumption by sensitive populations, without adverse human health effects. Planning for this study is currently underway.
- Data analysis is under way in a study examining the biological response among a group of 70 postmenopausal women who have a diet high in plant estrogens. This study will determine if diets high in phytoestrogens have a beneficial or detrimental effect on the development of postmenopausal disorders such as osteoporosis.

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Today, approximately 12 percent of Americans are over age 65. By the year 2025, this number is expected to grow to over 20 percent as life span extends well into the eighth decade. The mission of the NIA is to foster research that finds methods to extend years of productive life through improved health, lifestyle, and psychosocial status. The NIA's Nutrition and Aging Program contributes to this goal by sponsoring basic, animal model, clinical, and population-based studies to determine the ways that nutrition influences the onset and progression of aging.

Nutrition and aging research poses several unique challenges. The variation of physiological and behavioral measures increases with age. Because the rate of change in functional capacity and aging processes differs among individuals, those who reach old age are the most biologically heterogeneous of all age groups. The diversity observed in aging subjects results from a lifetime of environmental experiences superimposed on individual differences in genetic predisposition. Investigators in nutrition and aging must consider such factors as genetic variation, race, smoking status, physical activity, health and medication history, and social factors.

A most difficult problem is to separate those changes observed in old age that are due to inevitable aging processes from those that are manifestations of pathology. In some cases, like those related to the progressive loss of skeletal tissue, an aging process becomes pathological when bone density is reduced to a level where low trauma fractures can occur. Researchers also must determine if the magnitude of change in age-related parameters is clinically significant and which aging processes are detrimental to the health of older individuals.

RESEARCH DIRECTIONS

The NIA is continuing its efforts to expand the Nutrition and Aging Program. A key task in the expansion plans was to develop a rationale for research priorities. The NIA solicits input from the scientific community to aid in identifying the most important topic areas and directions for nutrition and aging research.

Nutrition research is supported in the four Extramural Programs: Biology of Aging, Behavioral Sciences, Geriatrics, and Neuroscience and Neuropsychology, as well as the NIA Intramural Programs. In 1991, the NIA created a nutrition coordinating office to give nutrition and aging research greater visibility and facilitate interaction and planning activities among the NIA programs.

Present research directions and areas of research priority in nutrition and aging are based on NIA staff evaluation of current research, advice from scientific advisors, and the results and recommendations from the nutrition and aging conferences. These include:

- Nutrient requirements and their age-dependent changes in older persons and animal models.
- Effects of age on physiological processes through which nutrients, drugs, and other nonnutrient substances are absorbed, metabolized, and excreted in humans and in analogous animal models.
- Effects of calorie reduction and of caloric excess resulting in obesity on longevity and age-related pathology.
- Nutritional factors associated with physiologic changes such as immunocompetence, neurologic function, body composition, sensory perception, control of appetite, macronutrient storage and utilization, rheology, and otolaryngology, endocrine control, and genetics.
- The role of nutrition factors in prevention and treatment of age-related degenerative diseases, including diabetes, osteoporosis, neurologic disorders, immune deficits, heart disease, cancer, and gastrointestinal diseases.
- Psychosocial aspects of nutrition, including studies of diet as a major factor contributing to the quality of life and how diet interacts with other lifestyle variables, including

exercise, smoking, and consumption of alcoholic beverages.
- Nutritional status of older Americans and special subpopulations of older people at special nutritional risk.
- Educational methods and program strategies that best promote adequate food consumption by older people.

OUTLOOK

A rapidly aging population makes it critical to find ways to maximize the span of good health and thereby improve the quality of life of older people. Nutritional factors hold great promise for realizing this goal. For these reasons, NIA's Nutrition Program supports research to clarify nutrition-aging interactions.

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NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

In 1950, major arthritis research programs were established within the National Institute of Arthritis and Metabolic Diseases through the Omnibus Medical Research Act. The research programs of the institute evolved over the decades, and its name eventually became the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) in 1980. The Health Research Extension Act of 1985 re-established the programs of the NIADDK as two institutes: the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the National Institute of Diabetes and Digestive and Kidney Diseases.

The NIAMS conducts and supports basic and clinical research on many of the most debilitating diseases affecting the U.S. population. These include the many forms of arthritis and numerous diseases of the musculoskeletal system and the skin, as well as research on the normal structure and function of joints, muscles, bones, and skin. Basic research involves a wide variety of scientific disciplines, including immunology, genetics, molecular biology, biochemistry, physiology, virology, and pharmacology. Clinical research addresses the fields of rheumatology, orthopedics, bone endocrinology, sports medicine, and dermatology. The NIAMS supports nutrition research related to these disease areas, scientific disciplines, and clinical fields.

RESEARCH DIRECTIONS

The NIAMS supports programs of research and research training in the fields of arthritis, musculoskeletal diseases, muscle biology, and skin diseases. Examples of ongoing nutrition research supported by the NIAMS are as follows:

- Studies to determine the optimal intake of calcium and the role of exercise in the development and maintenance of strong, healthy bones; for attaining a maximum adult peak bone mass; for minimizing the rate of bone loss in older individuals; and for the prevention of osteoporosis.
- Assessment of calcium absorption in women and its relationship to calcium intake, estrogen status, and age.
- Evaluation of bone density in patients with anorexia nervosa and determination of the extent to which recovery of bone density is possible in young adults.
- Research to determine the role of vitamin D metabolism in the pathogenesis of the vitamin D refractory diseases.
- Studies of the direct effects of vitamin D on bone cells in culture.
- Investigation of the effects of fluoride on the cellular and matrix components of bone.
- Research on the effects of omega-3 fatty acids, administered as fish oil supplements, on the pathogenesis of rheumatoid arthritis and other diseases characterized by chronic inflammation.
- Investigations to determine the functional relationship between essential fatty acid deficiency and skin conditions, such as abnormalities of desquamation (normal loss of bits of outer skin in scales) and defects in the skin's water barrier.
- Research on the mechanism of action and possible therapeutic uses of vitamin A and its synthetic derivatives, the retinoids, in skin biology.
- Studies of the effect of fatty acids and lipid metabolism on the differentiation of keratinocytes (skin basal cells).
- Studies of the effects of aluminum on bone formation and osteoporosis.
- Research on the photobiology of vitamin D.
- Support of arthritis, osteoporosis, and skin disease aspects of the Third National Health and Nutrition Examination Survey through an interagency agreement with the National Center for Health Statistics.

OUTLOOK

The institute's programs are organized to respond to public health needs as well as to the research opportunities and needs identified by working scientists in the academic community.

The NIAMS also enjoys a strong partnership with several private voluntary agencies dedicated to the control of relevant diseases. The concerted national effort that these forces bring into play will ensure continued progress toward more effective methods of treating and perhaps preventing these chronic diseases.

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NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS

The National Institute on Deafness and Other Communication Disorders (NIDCD) conducts and supports research and research training on normal mechanisms, as well as on diseases and disorders of hearing, balance, smell, taste, voice, speech, and language. NIDCD achieves its mission through a wide range of research performed in its own laboratories, a program of research grants, individual and institutional research training awards, career development awards, center grants, and contracts to public and private research institutions and organizations. The institute also conducts and supports research and research training that is related to disease prevention and health promotion. NIDCD addresses special biomedical and behavioral problems associated with people who have communication impairments or disorders. The NIDCD supports efforts to create devices which substitute for lost and impaired sensory and communication functions. The NIDCD Clearinghouse collects and disseminates information to health professionals, patients, industry, and the public on research findings related to deafness and other communication disorders.

Nutrition-related research is a component of the NIDCD chemical senses programs. The chemosensory programs are supported through a variety of funding mechanisms, including program project and center grants. The congressional mandate for the NIDCD chemosensory program includes the establishment of a data system derived from patient populations with disorders of smell and taste, including, where possible, data involving general populations for the purpose of identifying individuals at risk of developing those disorders. In addition, the NIDCD Clearinghouse will include the dissemination of information on chemosensory/nutrition disorders to facilitate and enhance knowledge and understanding of chemosensory/nutrition disorders by health professionals, patients, industry, and the public.

RESEARCH DIRECTIONS

What is ingested and rejected depends largely on its smell and taste. Ingestive choices can influence various disease states, such as hypertension and metabolic disorders. In turn, these disease states can affect chemosensory function and nutrient intake.

Examples of nutrition research supported within the fields of the chemical senses are as follows:

Human Studies

- Evaluate the association between nutritional status and problems of the senses of taste and smell in order to develop effective preventive interventions for individuals with various diseases.
- Study the relations between food intake, hormone levels, and taste sensitivity in pregnant women and their infants.
- Determine whether providing premature, tube-fed infants with sweet taste stimulation during feeding enhances growth and allows earlier progression to oral feeding.
- Identify the chemosensory disorders underlying inadequate food intake and complaints about bad tastes of certain foods by individuals with liver disease.
- Determine the role of mineral and vitamin deficiencies in patients with both taste disorders and the burning mouth syndrome.
- Determine the efficacy of the drug tetrahydrocannabinol in stimulating appetite in healthy persons and in persons with diseases such as cancer.
- Study the contributions of oral trigeminal sensation to taste and the perception of flavor.
- Determine the degree to which the genetically determined variation in taste sensitivity to phenylthiocarbamide and related chemicals is correlated with taste sensitivity and hedonic responses to foods and beverages containing sweet and bitter components.

- Study the genetically determined variation in the sensitivity and hedonic responses to the smell of androstenone, a natural steroid in bacon, celery, and truffles.

Animal and Other Basic Research

- Study the development of food preferences and aversions.
- Study the effects of perinatal restriction of dietary sodium on the early development of sodium taste.
- Determine whether salt appetite or the renal response following mineral corticoid administration to spontaneously hypertensive rats are related phenomena and, if so, due to the same natriuretic mechanism.
- Study the changes in ingestive behavior after damage to specific parts of the taste system in the hindbrain.
- Assess phenotypic differences in aversions to bitter substances in inbred strains of mice using behavioral, physiological, and molecular techniques.
- Elucidate the emergence of sodium chloride preference in a salt glutton strain of young rats and in a strain with a distaste of salt to determine whether their preferences are due to differences in amiloride-sensitive sodium transport in taste buds.
- Determine the mixture interaction effects of different tastants and olfactants in behavioral and neurophysiological studies.

OUTLOOK

Because nutrition often is a biomedically significant factor in studies of smell and taste, the NIDCD will continue to support chemosensory/nutrition research in the smell and taste programs. Because this research often is of trans-NIH relevance the NIDCD will continue to collaborate with other components of the NIH. This outlook reflects the recommendations of a task force of eminent scientists who formulated the National Strategic Research Plan of the National Institute on Deafness and Other Communication Disorders in January 1989.

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The recently established NCRR represents the merger of two former divisions: the Division of Research Resources (DRR) and the Division of Research Services (DRS). DRR and DRS both conducted programs providing resources for the performance of biomedical research: DRR developed and supported research resources extramurally through grants, and DRS provided research services directly to NIH intramural scientists. The NCRR will continue to integrate and extend these activities, which play a significant role in NIH's scientific programs, including nutrition-related research. The NCRR has seven extramural and four intramural components.

The seven extramural components are the Biological Models and Materials Resources Program, the Biomedical Research Support Program, the Biomedical Research Technology Program, the Comparative Medicine Program, the General Clinical Research Centers Program, the Research Centers in Minority Institutions Program, and the Research Facilities Improvement Program.

The four intramural components are the Biomedical Engineering and Instrumentation Program, the NIH Library, the Medical Arts and Photography Branch, and the Veterinary Resources Program.

Most of the extramural nutrition-related research is supported by the NCRR through its General Clinical Research Centers Program. The program funds a national network of 74 centers, usually organized as separate units within hospitals of academic medical centers. These centers provide clinical research resources for investigators supported by the categorical institutes of the NIH or by other peer-reviewed sources of funding. Resources include patient care facilities, with nursing and dietary support, and sophisticated laboratory technologies, including computer hardware and software. In addition, these centers introduce house staff and medical students to the interaction of basic and clinical research and the translation of research results into clinical practice.

Other extramural program components of the NCRR also support resources for nutrition-related research.

All of NCRR's intramural nutrition-related research is through its Veterinary Resources Program.

RESEARCH DIRECTIONS

The following are examples of NCRR's nutrition-related extramural research support:

- Studies of malabsorption in patients with AIDS.
- Research on the role of food hypersensitivity in atopic dermatitis.
- Research on affective and appetite symptoms associated with premenstrual syndrome.
- Studies to evaluate dietary therapy of X-linked adrenoleukodystrophy.
- Studies on dietary cholesterol effects on plasma lipoproteins.
- Investigations of metabolic regulation and nutrition in aging humans.
- Studies on nutrient transfer into human milk and body composition in lactating and nonlactating women.
- Studies of dietary therapy of gyrate atrophy of the choroid and retina.

The following are examples of recent collaborations of NCRR intramural scientists (in the Veterinary Resources Program) with other NIH scientists and outside institutions in animal nutrition research:

- Investigations by the NIA to determine the influence of a calorie-restricted diet on the longevity of nonhuman primates.
- Long-term toxicology research by the NIEHS that requires a specially developed diet for the long-term maintenance of rodents.
- Studies on the influence of various dietary constituents on hypertension in the spontaneously hypertensive rat.
- A collaborative study with the Clinical Center on the relationship between

lipoprotein and apoprotein phenotypes of the Watanabe Heritable Hyperlipidemic (WHHL) rabbit and diet.

OUTLOOK

The NCRR will continue to support resources essential to the conduct of biomedical research, that will lead to improved human health.

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JOHN E. FOGARTY INTERNATIONAL CENTER FOR ADVANCED STUDY IN THE HEALTH SCIENCES

Established in 1968, the FIC supports fellowships to enable U.S. and foreign scientists to pursue their research interests in U.S. and foreign laboratories, providing an opportunity for them to exchange information and research experiences in all fields of the biomedical and behavioral sciences, but not directed to any specific research area. Funding decisions are determined by the excellence of the individual research applications and the potential for increased international research collaboration.

There are three distinct fellowship programs:

The Senior International Fellowship (SIF) Program is intended to enhance the exchange of ideas and information about the latest advances in the health sciences and to improve the research, educational, and clinical potential of the U.S. nominating institutions. These U.S. scientists spend from 3 to 12 months in foreign laboratories, in as many as three separate terms utilized over a 3-year period, pursuing projects of mutual interest to the fellows and the foreign host scientists. Between 40-50 awards are made annually.

The International Research Fellowship (IRF) Program was established to stimulate health-related research by enabling foreign postdoctoral biomedical or behavioral scientists to extend their research experience by working with distinguished U.S. scientists on problems of mutual interest. About 100 awards are made each year to foreign scientists who are in the formative phase of their research career. Approximately two-thirds of the fellows receive 2-year awards. Applications are made through their home country nominating committees.

The Foreign-Funded Fellowship (FFF) Program is supported by specific foreign countries. They provide opportunities for scientists to conduct collaborative research in the country that provides funding. The purpose of this program is to enhance the exchange of research experience and information in the biomedical, behavioral, and health sciences. Participating countries are Finland, France, Federal Republic of Germany, Ireland, Israel, Japan, Norway, Sweden, Switzerland, Taiwan, and the United Kingdom.

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The NCNR, established in April 1986 as an NIH component, supports research in nutrition as it relates to health promotion, disease prevention, and acute and chronic illness and disabilities. The goal of nursing research is to improve nursing care for all segments of society by expanding the scientific base for nursing practice, focusing on the full spectrum of human health and disease, from the prenatal stage to old age.

Although behavioral nutrition is not the primary focus in most of the nutrition-related studies at NCNR, investigators collect data on nutritional intake and behaviors affecting the utilization and intake of nutrients. Current NCNR nutrition highlights are primarily in infant health, health promotion, obesity, and human immunodeficiency virus (HIV) infection.

RESEARCH DIRECTIONS

The NCNR has developed the research structure needed to make progress in priority areas that address specific health concerns of society. The nursing research priority areas with nutrition research potential include:

- Improved feeding techniques for low birth weight infants to provide needed nutrition and support weight gain.
- Assessment of nutritional needs and related issues in elderly persons who require long-term care.
- Assessment of the type, severity and causes of nutrition related problems in AIDS patients.
- Health behavior development in children and adolescents including health promoting and health compromising behaviors related to dietary intake and eating patterns.

OUTLOOK

The challenge that lies ahead for NCNR is to encourage a strong research environment that will produce the scientific knowledge needed to guide nursing practice. Future studies will build on the basic sciences, integrating them with the biological, behavioral, and social correlates that influence nutritional health and disease. Collaboration with other NIH components is of continuing importance.

For more information on the NCNR nutrition program, contact:

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NATIONAL CENTER FOR HUMAN GENOME RESEARCH

The National Center for Human Genome Research (NCHGR) was established on October 1, 1989. Its goal is to map and sequence the genome of humans and important model organisms and examine the ethical, legal, and social issues raised by the acquisition of this information. The Human Genome Initiative is a worldwide research effort. The NCHGR is the NIH representative in this effort. A centrally coordinated project is believed to be the most efficient and least expensive way of obtaining information on the genome.

Information obtained from the Human Genome Project will be a tremendous resource for studies of gene structure and function. It will increase manyfold our understanding of the genetic aspects of human health and disease. Improved understanding will eventually provide insights into the prevention and treatment of many human diseases--not only the 3,000 known inherited disorders but also those that result from interactions of our genes, environments, and behavior.

Realizing these benefits will require professional and public deliberations over an important set of bioethical questions about the responsible use of genetic information. The Genome Center recognizes that a certain level of public and professional understanding of both the scientific aspects of the Project and the policy questions its applications may raise are crucial to realizing the Project's ultimate public benefits. Assessment of the current level of public and professional understanding in these areas, or where the greatest deficiencies lie, is necessary in order to orient the focus of the NCHGR.

RESEARCH DIRECTIONS

In FY 1990, the NCHGR and the Department of Energy issued a joint research plan for the first 5 years of the Human Genome Project. Five-year goals have been identified for the following areas, which together encompass the human genome project:

- Mapping and Sequencing the Human Genome
- Mapping and Sequencing the Genomes of Model Organisms
- Data Collection and Distribution
- Ethical, Legal, and Social Considerations
- Research Training
- Technology Development
- Technology Transfer.

For more information on the NCHGR nutrition activities, contact:

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The Warren Grant Magnuson Clinical Center (CC), located on the NIH Bethesda campus, is the world's largest hospital devoted solely to clinical research.

This 500-bed facility, which was completed in 1953, is designed to allow NIH's intramural scientists to bring research closer to the patient's bedside. Each year, about 5,000 individuals come from all over the world to participate, upon referral by their physicians, as inpatients in clinical studies at the NIH.

The Ambulatory Care Research Facility (ACRF), added in 1981, provides additional space for laboratories for the CC's rapidly growing outpatient program. Each year there are about 72,000 outpatient visits to the ACRF. The ACRF allows the NIH to admit the large number of patients who, though ill enough to require care, do not require hospitalization. Such an arrangement has two clear benefits: a greater volume of patients can be treated by NIH physicians and a greater number of research studies can be initiated.

Institutes conducting clinical research at the NIH are allocated inpatient beds according to their program needs. At present, the NCI is assigned the largest number of beds in the CC, with the NHLBI second. No matter which institute authorizes admission, the patient is served by an extensive support system. The health care team routinely includes nurses, physicians, dietitians, social workers, therapeutic recreation specialists, and rehabilitation therapists; where appropriate, it may include other personnel such as chaplain or interpreter. Further support to patients is offered by CC medical departments equipped to meet the needs of biomedical research and patient care. Characterized by state-of-the-art technology, these include Transfusion Medicine, Pharmacy, Diagnostic Radiology, Rehabilitation Medicine, Nuclear Medicine, Critical Care Medicine, and Clinical Pathology.

The Nutrition Department of the Warren Grant Magnuson Clinical Center supports most of the nutrition-related research at the Clinical Center.

RESEARCH DIRECTIONS

The Nutrition Department of the Clinical Center implements nutrition components of protocols generated by the various institutes. The Nutrition Department dietitian collaborates with clinical investigators in developing protocols in which dietary components affect the interpretation of the study. The Nutrition Department aids in conducting nutrition research in the following ways:

- **Special Nutrition Regimens for Research Protocols.** Numerous intramural research protocols require nutritional intervention. The research dietitian is active in direct implementation of nutrition components of protocols and in provision of comprehensive nutritional care to patients on research protocols. Implementation of protocol requirements includes provision of controlled nutrient intakes for various disease states (e.g., eating disorders, gyrate atrophy, morbid obesity, and Parkinson's disease) and for drug-related studies. Test diets are provided, either as an integral part of a protocol or as a diagnostic procedure. Other research-related activities include obtaining anthropometric measurements to assess body composition, diet counseling for protocol-specific diets with subsequent determination of compliance, developing and implementing nutrition education classes to support protocol requirements, developing questionnaires to assess dietary intake patterns, and providing dietary regimens for studies requiring assessment of appetite in relation to specific drug therapies.
- **Metabolic Balance Studies.** The metabolic balance study is a method of investigating the metabolism of chemical elements of food constituents by determining the loss or retention of these substances in the body. These studies are carried out utilizing a

metabolic kitchen capable of serving 10 patients at one time.

- **Nutrient Data Collection Studies.** Collection of nutrient data from the free-living population (outpatients) is another research collaboration service provided by the Clinical Center Nutrition Department. Research participants are taught standardized record-keeping techniques for recording food intake. To assist in accuracy, participants quantify their consumption of food by weights or by measures in standard household measures. Completed records are reviewed with the participant and subsequently computer-analyzed by the Nutrition Coordinating Center of the University of Minnesota.

For more information on the CC nutrition program, contact:

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DIVISION OF LEGISLATIVE ANALYSIS

The DLA, OD, is the focal point of responsibility for advising the Director, NIH and other senior executive staff of the NIH on legislative developments relevant to NIH programs, the need for changes in the statutory base of NIH activities, and the development of new legislative proposals. In addition, the office coordinates responses to NIH congressional communications; provides NIH liaison on legislative matters with the DHHS, the Congress, and other bodies; and prepares or coordinates the preparation of testimony or statements for use by the staff of the OD, NIH before congressional committees or groups. DLA also develops special staff documents, such as NIH position papers, legislative histories, briefings, and other materials, that concern NIH interests, activities, and relationships.

In this capacity DLA has served as a liaison between the NCC and the Congress and has provided information and guidance on several legislative issues this year. In FY 1990, DLA was instrumental in working with the NCC on pending nutrition legislation such as food labeling and nutrition monitoring, obesity research issues, and FY 1991 appropriations bills.

Over the past year, DLA has worked with the NCC to help establish improved relationships with congressional staff members in order to provide the best possible information to Congress about the NIH efforts in nutrition research. Congress continues to emphasize the need for a coordinated effort between the USDA and the NIH in areas of nutrition research, nutrition monitoring, and issuance of dietary guidance. The NIH has historically endorsed the importance of such coordination and collaboration on nutrition research and training, as evidenced by its trans-NIH coordination of biomedical nutrition research and training programs and by the many interagency cooperative efforts outlined in this report.

For additional information on DLA activities, contact:

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Section 3. Highlights of Biomedical and Behavioral Programs in Nutrition Research and Training

HIGHLIGHTS OF BIOMEDICAL AND BEHAVIORAL PROGRAMS IN NUTRITION RESEARCH AND TRAINING

The NIH nutrition research program includes extramural and intramural research and research training and research manpower development. The major component of the program is the extramural research program carried out at various universities, in graduate science departments, principally in departments of nutrition; and medical, dental, and other health professional schools, especially schools of public health. A large portion of the research projects is based on ideas developed and submitted by individual investigators from research institutions throughout the nation and the world. Most of the intramural program is carried out on the NIH campus in Bethesda, Maryland, in laboratories and at the Clinical Center. The intramural program of the NIA is carried out at the Gerontology Research Center (GRC) in Baltimore, Maryland; the NCI established a Laboratory for Nutrition and Cancer Research in Frederick, Maryland; some intramural nutrition research is conducted by the NIDDK at the Phoenix Epidemiology and Clinical Research Branch in Phoenix, Arizona; and the NIEHS is located in Research Triangle Park, North Carolina.

Three major funding mechanisms serve as administrative instruments for accomplishing NIH program goals through the efforts of scientists outside the NIH. These extramural mechanisms are financial assistance awards (grants and cooperative agreements) and acquisition awards (contracts), as described in appendix J. Awards are made to extramural institutions following a carefully executed scientific review known as the peer-review process. Studies within the NIH intramural research program are also subject to scientific review.

The intramural and extramural research highlighted in this section does not provide a comprehensive list of the approximately 2,400 nutrition research and training projects funded by the NIH in FY 1990, nor is it inclusive for each topic presented. Rather, for this issue of the annual report, we have chosen to present highlights of nutrition research on certain selected topics and highlights of nutrition research conducted under center grants and program project grants, as well as highlights of national nutrition monitoring research, technology transfer, and training to emphasize the diversity of the field.

HIGHLIGHTS OF NUTRITION RESEARCH: SELECTED TOPICS

The topical areas of NIH-supported nutrition research included in this report transcend institute boundaries. They illustrate nutrition's role in preventing some of the most common diseases and public health problems that affect our population and range from basic nutritional science to dietary treatment of disease.

In the *12th Annual Report of the National Institutes of Health Program in Biomedical and Behavioral Nutrition Research and Training, FY 1988* (NIH Publication No. 89-2092, 1989), research on nutrition and AIDS; nutrition and the human genome; nutrition and behavior, including obesity and anorexia; and nutrition in the prevention of stroke, diabetes, and osteoporosis was highlighted. The focus in the *13th Annual Report of the National Institutes of Health Program in Biomedical and Behavioral Nutrition Research and Training, FY 1989* (NIH Publication No. 90-2092, 1990) was on the role of nutrition in the prevention of obesity, cardiovascular disease, and osteoporosis in minority populations and the role of nutrition in rare diseases and conditions. In this year's report, research related to the *Healthy People 2000* nutrition priority area objectives, nutrition and neurological function, nutrition and molecular biology, and nutrition in acute and chronic illness and injury is highlighted.

Nutrition Research Related to the Healthy People 2000 Objectives

One of the major events of 1990 was the release by the PHS of *Healthy People 2000: National Health Promotion and Disease Prevention Objectives for the Nation* (DHHS Publication

No. [PHS] 91-50212) in September. *Healthy People 2000* offers a vision for the new century, characterized by significant reductions in preventable death and disability, enhanced quality of life, and greatly reduced disparities in the health status of populations within our society. It is the product of a national effort, involving professionals and citizens, private organizations and public agencies from every part of the country. Work began on the report in 1987 with the convening of a consortium that grew to include almost 300 national membership organizations and all the state health departments. The objectives described in the report lay out a series of national opportunities to dramatically cut health care costs, to prevent the premature onset of disease and disability, and to help all Americans achieve healthier, more productive lives.

Among the objectives detailed in the report are 21 that address nutritional concerns. The report notes that, in ways often interrelated with patterns of physical activity, dietary factors are associated with 5 of the 10 leading causes of death in the United States: coronary heart disease , some types of cancer, stroke, noninsulin-dependent diabetes mellitus, and atherosclerosis. The 1988 *Surgeon General's Report on Nutrition and Health* (DHHS [PHS] Publication No. 88-50210) concluded that for the 2 out of 3 Americans who neither smoke nor drink, eating patterns may affect long-term health prospects more than any other personal choice. In general, excesses and imbalances of some food components in the diet have replaced once prevalent nutrient deficiencies as the principal concern.

The *Healthy People 2000* nutrition objectives are consistent with the joint DHHS/USDA *Dietary Guidelines for Americans* (USDA Home and Garden Bulletin No. 232, Third Edition, 1990) which advise consumption of a variety of foods; maintenance of healthy weight; choice of a diet low in fat, saturated fat, and cholesterol, and with plenty of fruits, vegetables, and grain products; use of sugar, salt, and sodium only in moderation; and moderation if alcoholic beverages are consumed. Two nutrition objectives have been highlighted as "flagship" objectives: the reduction of overweight and the reduction of dietary fat intake. Overweight affects about 26 percent of the population and is especially prevalent in women and in poor and minority populations. Prominent among the many dietary components involved in diet and health relationships is the disproportionate consumption of foods high in fats, often at the expense of foods high in complex carbohydrates and dietary fiber that may be more conducive to health.

Other objectives target increasing consumption of vegetables, fruits, and grain products; decreasing sodium consumption; increasing calcium intake, in particular for young people and pregnant or lactating women; increasing breastfeeding; increasing the use of feeding practices that prevent baby bottle tooth decay; reducing iron deficiency and growth retardation in children; providing useful and informative nutrition labeling for all food products; increasing availability of low-fat products; improving identification of low-fat, low-calorie food choices in restaurants; paying more attention to nutrition education and food choices in schools; making better use of worksites for nutrition education and services; and encouraging a stronger focus by primary care physicians on the nutritional practices of their patients. Also identified in the report are surveillance and data needs, as well as research needs.

The NIH, together with the FDA, served as co-lead for the development of the *Healthy People 2000* nutrition priority area objectives. The NIH Task Force on the Nutrition Priority Area Year 2000 Health Objectives for the Nation (see appendix B) continues to work towards NIH implementation activities for *Healthy People 2000* nutrition objectives. The institutes and centers of the NIH support a wide range of nutrition research directed towards an understanding of the relationships of dietary patterns and individual nutrients to the prevention of disease and promotion of health. Highlights of some selected research projects related to topics addressed in the *Healthy People 2000* nutrition objectives are contained in the following section.

Obesity Research

Obesity is very prevalent in the United States, affecting approximately 34 million adults ages 20-74 years. Obesity (or severe overweight) increases the risk for high blood cholesterol, high blood pressure, and diabetes and, hence, for diseases for which these conditions are risk factors. It also increases the risk for gallbladder disease, for osteoarthritis of weight-bearing joints, and for some types of cancer and has significant psychosocial consequences. The high prevalence of obesity and its physical and mental health consequences motivate the high public health priority placed on its prevention.

The prevalence of obesity is disproportionately high in some subgroups of the population. National survey data indicate that the highest rates are observed in low-income and minority groups, especially low-income women and black and Mexican-American women. Prevalence rates are also strikingly high in some Native American population groups. Research needs identified in the area of obesity include examination of the relationship of body weight, total body fat, and body fat distribution to health outcomes; the epidemiology of weight gain and successful weight loss; and the health effects of weight loss and regain.

- The National Growth and Health Study (NGHS)

Obesity is regarded as a significant predictor of coronary heart disease (CHD) and is also one of the major public health problems in black women. Obesity in black women has been suggested as a major contributor to higher cardiovascular disease (CVD) mortality among black compared with white adult women.

The National Growth and Health Study is investigating, over 5 years, the occurrence of obesity in black and white girls, age 9 and 10 at baseline, the predictors of transition to the obese state, the correlates of this transition, and the relationship of this transition to other CHD risk factors. Three clinical sites and a coordinating center were selected for this program in 1985. The study is currently in its fourth year of followup examinations. The participation rates of NGHS have been outstanding, with more than 90 percent of the original cohort returning for visits throughout the third year of followup. Enrollment was completed for 2,379 girls, ages 9 and 10 at baseline (49 percent white and 51 percent black) and at least some information on approximately 4,000 parents and guardians. Measurements include pulse, blood pressure, skinfolds and girths, bioelectric impedance, blood lipids, dietary intake, physical activity, and psychosocial information from both the girls and their parents which includes questions on body image, perceived ideal body image, and parental and peer influences.

Baseline data revealed that on average black girls were slightly older, taller, heavier, had higher body mass index, greater skinfolds, and were at a higher pubertal stage than white girls. Black girls reported consuming more calories, more grams of fat, and higher percent of calories from fat. Black girls reported watching considerably more television--12 hours per week more--than white girls. Systolic and diastolic blood pressures were higher in black girls compared to white girls. Total cholesterol, low density lipoprotein (LDL)-cholesterol, and apo-B were similar in both races. Triglycerides were higher in white girls, while high density lipoprotein (HDL)-cholesterol and apo-A1 were higher in black girls.

Results from the psychosocial questionnaires showed that compared to white girls, black girls were more content with their present weight, were more satisfied with their appearance, and were more satisfied with their separate body parts. Black girls scored somewhat lower on the athletic competence, behavioral conduct, and scholastic competence subscales and higher on the physical appearance subscale on the Harter scales for self-concept. There were no significant differences by race on the global worth or social acceptance subscales. When analyzed by household income and parental education, obesity was inversely associated with socioeconomic status in white girls but not in black girls, where obesity occurred at the same rate across household income and education.

Results from the second year of followup show that over 2 years black girls gained 1.9 kg more weight than white girls while the height change between the two races differed only by 0.1 cm. Increase in body mass index and skinfolds was 0.6 kg/m^2 and 2.9 mm greater, respectively, in black girls compared to white girls. There were no significant differential changes in blood lipids between the black and white girls over two years. Blood pressure increases over two years were marginally greater in black girls compared to white girls.

In terms of obesity, defined as above the 85th percentile of body mass index based on age-sex specific reference data from the National Center for Health Statistics national population sample, at baseline 31.1 percent of the black girls were obese compared to only 21.2 percent of the white. These percentages grew slightly to 34.6 percent and 22.0 percent, respectively, by 2 years of followup.

- Regulation of Body Weight in Humans

In both obese and never-obese human subjects, the physiological mechanisms responsible for the long-term regulation of body weight have been investigated by examining the metabolic effects of experimental perturbations of body fatness. Individuals are admitted to a clinical research center for periods ranging from 4 months to 2 years. When body fat is increased or decreased by 10 percent or more, metabolic changes occur which tend to return body fat to its initial status. Weight gain is accompanied by an increase in total energy requirements in excess of that due to increased body size. This increase in energy expenditure appears to be due to an increased energy need for skeletal muscle activity. Conversely, achievement of weight plateaus below usual is accompanied by a decrease in energy need for skeletal muscle activity. These studies support the existence of a regulatory system for the control of body fat. This work has, for the first time, demonstrated compensatory changes in energy efficiency which operate to stabilize body weight and fatness over long periods of time. These experiments suggest that obese and nonobese individuals differ not only in the nature or intensity of their responses to perturbation of body weight, but in the degree of body fatness around which they regulate. These studies identify the changes in energy efficiency which are the reasons for the extraordinary difficulties experienced by those attempting to sustain weight loss long-term. They also indicate that skeletal muscle may play a much more important role in the regulation of energy efficiency than was heretofore believed. The degree of fatness about which an individual regulates is probably determined by an interaction of environmental and genetic influences.

- Energy Regulation and Changes in Body Composition in Old Age

The benefits of upper body weight loss were demonstrated in a study on the effects of body composition and exercise capacity on glucose tolerance, insulin, and lipoprotein lipids in a group of 77 healthy, nonsmoking white males, ages 46 to 73 years. A deterioration in glucose tolerance and increased insulin sensitivity are associated with increased risk for both diabetes and heart disease. Both the longitudinal and cross-sectional data indicate that body composition (waist-hip ratio or percent body fat) is a more important determinant of metabolic function (lipoprotein lipid profiles, insulin levels, and glucose tolerance) than either age or aerobic capacity ($V0_2$ max). In a related study of 146 healthy men and women in their sixties, the plasma level of HDL_2 cholesterol was inversely correlated with the waist-hip ratio, the plasma insulin level, and glucose intolerance.

Growing evidence suggests that the association of obesity with mortality or morbidity after the sixth decade is minimal, or at least is much weaker than during the third through the fifth decades. However, new work shows that low body weight in old age appears to be a risk factor for mortality as well. In a study of 4,710 white NHANES I respondents, a body mass index (BMI) of less than 22 is associated with elevated mortality for men over age 55 and women older than 65. The data were adjusted for current smoking and underlying disease. The added risk is in the range of 30 to 60 percent. The investigators conclude that the accepted definition for overweight (BMI>27.8 for males and BMI>27.3 for females) may be inappropriate for older people who do not have weight-related conditions. Definitions of obesity that allow for an increase in weight with aging, based on the criterion of optimum survivorship, have been recommended. These studies have important clinical implications as well as forming a potential basis for public health recommendations. Mechanistic studies are now needed to explain their significance to age-related chronic diseases and establish links to aging processes.

- Genetics and Obesity

There are great differences among people of a given age and sex in body fat content, as well as its regional distribution. Although the reasons for such differences are not completely known, studies have been conducted which have provided strong support that inheritance is a factor in obesity, as well as in regional fat distribution.

Researchers have evaluated the differences in weight gain and regional distribution of fat among individuals in a long-term overfeeding program which assesses the contributions of genetic and nongenetic sources of variation in changes in body fat content. The participants in the study included 12 pairs of identical twins. Initially, the energy requirements of each individual were evaluated. Thereafter, their diets were adjusted to provide an excess of 1,000 calories daily, 6 days per week. Over a 100-day period, body weight increased significantly in all subjects, with a mean weight gain of 8.1 kilograms. However, the weight gain ranged from 4.3 kilograms to 13.3 kilograms. Body composition also changed significantly during the study. Both fat and fat-free (or muscle) mass increased, but the gain in fat mass was greater. The increase in weight and total fat mass resulted in a significant increase in resting heart rate and diastolic blood pressure, with systolic blood pressure being unaltered.

Regional fat distribution also changed during the study. The amount of subcutaneous fat--as estimated by skinfold thicknesses--increased on both the trunk and limbs, but accumulated slightly more on the trunk. Both the waist and hip circumference increased significantly. However, the waist increased more than the hip circumference, causing an increase in waist-to-hip ratio. Overfeeding also increased the amount of visceral or intraperitoneal fat, with a wide range of variation among subject pairs. In all methods of assessing biological and physiological changes within this study, the responses observed within each identical twin pair showed significantly less variance than among pairs of identical twins. This indicates a strong genetic element.

The changes in body weight, body composition, trunk fat, and visceral fat deposition varied among the twin pairs studied. Differences between the high weight gainers and the low weight gainers were approximately threefold. Individual differences in weight gain due to overfeeding has been demonstrated previously; however, in this study, the degree of overfeeding was identical, and the duration was long enough to assess changes in body composition, as well as regional fat distribution. This allowed for an excellent and accurate evaluation of the genetic influence. These results strongly support the view that there are individual differences in the tendency towards the development of obesity and the distribution of body fat. Moreover, this shows that these differences are at least partly genetically related.

In another study, identical and fraternal twins who were raised either together or apart were compared for indices of obesity. Those evaluated were: 99 pairs of identical twins raised apart, 154 pairs of identical twins raised together, 218 pairs of fraternal twins raised apart, and 208 pairs of fraternal twins raised together. Consistent with other previous studies, as well as the smaller but more biochemical and physiological study reported above, these epidemiological studies showed that there was a strong hereditary influence on the body mass index (a measure of obesity). The intrapair agreement among identical twins was more than twice as good as that among fraternal twins. Importantly, these studies showed that childhood environment did not contribute significantly to the variation in body mass index. This indicates that obesity's environmental influences are not attributable to shared family influences, but are unique to the individual person.

These studies indicate the importance of genetic factors to the development of obesity. Genetic factors probably account for 70 percent of the susceptibility the problem. Most noteworthy was the striking similarity of changes within pairs in abdominal visceral fat. This observation is particularly important, because people with a tendency to accumulate abdominal fat or an increased waist-to-hip ratio, have an increased risk of diabetes, hyperlipidemia, hypertension, and mortality. In view of the evidence linking abdominal obesity to these associated diseases, the significant increase in diastolic blood pressure in association with the modest increase in total body fat observed during the overfeeding study is especially striking.

- Nutrient-Gene Interactions

Investigations of the mechanisms of body weight regulation in men of normal body weight have been initiated. Changes in total and resting energy expenditure, body composition, and subsequent voluntary nutrient intakes in response to overeating were assessed while subjects were consuming a typical diet. On the average, 85 to 90 percent of excess energy intake was deposited (with 87 percent of this amount in fat and 13 percent in protein, on the average). There appears to be no detectable difference among individuals in susceptibility to energy deposition. The resting metabolic rate in both fasting and fed states increased in overfeeding, although some of this energy expenditure was associated with nutrient assimilation. There was no observed significant increase in energy expenditure related to physical activity or thermal regulation during the overfeeding period. Consequently, energy expenditure did not substantially adapt to the increased energy intake. However, significant decreases in voluntary energy intake and fat intake occurred after the period of overeating, indicating that adapted changes in nutrient intakes can contribute significantly to body weight regulation after overeating.

Effects of Dietary Fat

Dietary fat contributes more than twice as many calories per unit of weight as carbohydrates or protein. Currently, the average American diet exceeds the recommended level of 30 percent of calories from fat. Considerable evidence links diets high in fat with increased risk of obesity, some types of cancer, and possible gall bladder disease. Saturated fat intake is strongly and consistently related with increased risk of CHD. The mechanisms of action of dietary fat effects on health are under investigation.

- Dietary Polyunsaturated Fatty Acids and Eicosanoids

The mechanism leading to the markedly lower plasma triglyceride and very low density lipoprotein (VLDL) levels in both normal and hypertriglyceridemic subjects after consuming fish oils has been investigated. The kinetics of VLDL-triglycerides were determined over a 48-hour period following the injection of tritiated glycerol. Fish oil diets were shown to reduce the VLDL-triglyceride synthetic rate and increase the fractional catabolic rate for VLDL-triglycerides. Concurrently, there was a 66 percent reduction of plasma triglyceride levels, resulting largely from a decrease in VLDL-triglyceride levels. The VLDL-cholesterol:triglyceride ratio increases during the fish oil diet, suggesting that smaller VLDL particles were present. Because these particles would be expected to leave the VLDL fraction more rapidly than in larger particles, the investigators concluded the hypotriglyceridemic effect of fish oil appears to be caused primarily by an inhibition of VLDL-triglyceride synthesis.

- Studies of Omega-3 Polyunsaturated Fatty Acids in Thrombosis and Cardiovascular Diseases

Various studies have been conducted on the effect of omega-3 fatty acids on blood cells. Dietary omega-3 fatty acids incorporated in membrane lipids of megakaryocytes and platelets in mice are potent inhibitors of platelet adhesion in humans, retard coronary thrombosis and vasoconstriction in dogs, and induce antithrombotic effects in nonhuman primates.

Omega-3 fatty acids are incorporated to the same extent in human plasma lipoproteins regardless of the chemical form (ethyl ester or glyceride) of the ingested acid. These acids are converted to a multitude of eicosanoids that were detected in human urine, and they have controversial effects on regulation of renal functions and blood pressure. The lipoxygenase products of omega-3 fatty acids play important roles in the permeability and function of cultured human cerebral microvessel endothelium.

Studies of the effects of omega-3 fatty acids on cardiac function have indicated that cardiac contractility can be regulated in response to omega-3 fatty acid effects on cardiac glycosides. Omega-3 fatty acids augment the effect of cyclosporine in retarding acute rejection following cardiac transplantation in animals.

Other investigations have examined the effects of omega-3 fatty acids on lipoprotein enzymes and as substrates for the formation of lipoprotein particles. VLDL particles produced following liver perfusion are highly enriched with omega-3 fatty acids, which could be important in the mechanisms involved in the hypotriglyceridemic effects of omega-3 fatty acids. Omega-3 fatty acids also play a regulatory role in the secretion of lipoprotein lipase of adipocytes.

- Fish Oil and Restenosis

An ongoing clinical trial is testing whether a daily supplement of 8 g of n-3 polyunsaturated fatty acids of marine origin will reduce the rate of restenosis of coronary lesions following percutaneous transluminal coronary angioplasty (PTCA). The ethyl esters of the fish oil are given for a period of 2 weeks prior to angioplasty and for 6 months following angioplasty. Quantitative computerized angiography is done at baseline (immediately after the PTCA) and at 6 months, and restenosis is defined as a loss of 50 percent of the gain achieved at PTCA and less than 50 percent of the luminal diameter remains patent. Over 400 patients are expected to complete the study.

- Dietary Fat and Resistance of LDL Particles to Oxidative Modification

Lipoproteins rich in polyunsaturated fatty acids should be more susceptible to oxidative modification than lipoproteins rich in saturated fatty acids. When the oxidative modification hypothesis was first proposed, it seemed to contradict the practice of using diets rich in polyunsaturated fats to reduce the risk of coronary artery disease events. Yet, if the hypothesis is correct, patients on such diets would presumably have LDL particles relatively enriched in polyunsaturated fatty acids that would be more susceptible to oxidation and potentially more atherogenic. On the other hand, diets rich in polyunsaturated fats do lower total plasma LDL levels, and the benefit gained thereby may overbalance any deleterious consequences of having LDL rich in polyunsaturated fatty acids. Monounsaturated fatty acids do not generate low molecular weight fragments on oxidation as do the polyunsaturated fatty acids. Moreover, diets rich in monounsaturated fatty acids have been shown to lower plasma cholesterol levels just as effectively as diets rich in polyunsaturated fatty acids.

To test the hypothesis that the administration of a diet rich in oleic acid would, in fact, lead to LDL resistant to oxidative modification, rabbits were fed diets containing 10 percent by weight of either a special vegetable fat containing more than 80 percent oleic acid or ordinary sunflower oil, rich in linoleic acid. The fatty acid composition of the LDL samples after 6-10 weeks on the diet tended to approach that of the dietary oil. The LDL from rabbits fed an oleic acid-rich diet were remarkably resistant to oxidative modification measured either in terms of the rate of diene conjugation or in terms of the amount of thiobarbituric acid-reactive substances generated. Furthermore, after identical exposures to pro-oxidant conditions *in vitro*, the linoleic acid-rich LDL were taken up and degraded rapidly by macrophages (at least at the same rate as LDL from control rabbits on their usual chow diet), whereas the oleic acid-rich LDL showed very little or no increase in susceptibility to degradation by macrophages. The oleic acid-rich LDL exposed to oxidation in the presence of copper ion, thus, did not undergo the structural changes that generate configurations recognized by scavenger receptors on the macrophage. Such LDL presumably would be less atherogenic.

- Effects of Dietary Cholesterol, Fat, and Fiber on Plasma Lipoproteins

In humans, postprandial lipidemia is greater and more prolonged after fat loads containing saturated fat than after fat loads containing unsaturated fat, thus, possibly exposing the vascular system to atherogenic chylomicron remnants for longer periods of time. American Heart Association (AHA) Step One diets enriched in polyunsaturated fatty acids had only slightly greater ability to lower serum cholesterol than AHA Step One diets enriched in monounsaturated fatty acids; most cholesterol lowering seems to result from the reduction in saturated fat intake. High cholesterol diets seem to have little effect on plasma cholesterol levels in humans unless dietary fat is saturated. Older persons secreted more ApoB in the VLDL fraction and less ApoB in the LDL fraction than younger individuals, but cholesterol-lowering diets appear to be equally effective across the adult age range.

LDL cholesterol levels generally are lower when high soluble fiber diets are consumed. High-fiber, low-fat experimental diets designed to be isocaloric often are associated with 1-2 kg weight losses nevertheless. Diets containing either 20 or 30 percent fat calories lowered plasma cholesterol levels to the same degree over a 20-week period. The relationship of ApoE phenotypes to the plasma cholesterol response to dietary cholesterol or various types of dietary fiber is under active exploration.

Studies in nonhuman primates are actively characterizing groups of baboons and African green monkeys that are hypo- or hyper-responders to dietary manipulations designed to raise plasma cholesterol levels prior to studies of genetic control mechanisms, cholesterol absorption, and lipid metabolism.

- Dietary Fat and Tumorigenesis

Several epidemiological studies have demonstrated that a high intake of dietary fat is generally correlated with an increased colonic cancer risk in humans. The results of animal studies suggest that the effect of dietary fats on tumor promotion not only depends on the amount of dietary fat consumed, but also on the types of polyunsaturated and saturated fats consumed. Sources of dietary fats containing high levels of unsaturated fatty acids, such as corn oil or safflower oil, have been shown to increase chemically-induced colon tumors, whereas sources of dietary fats containing high levels of saturated fatty acids such as olive and coconut oil had no tumor-enhancing effect. While the mechanism for the enhancement of tumorigenesis by dietary fat is a subject of intense investigation, the precise role of dietary fat remains to be elucidated.

In order to clarify the mechanism by which dietary fat enhances tumorigenesis, investigators are exploring the possibility that unsaturated fatty acids enhance tumorigenesis via the formation of biologically active autoxidation products. Because the induction of ornithine decarboxylase and stimulation of DNA synthesis are associated with tumor promotion, investigators on one grant have determined the structural features of oxidized fatty acids that are required for such activity. The mitogenic activity of hydroperoxy and hydroxy fatty acids derived from oleate and stearate were investigated as well as ricinoleic acid and the alpha, beta-unsaturated ketone derived from oleic acid. It was found that a carbon-carbon double bond adjacent to an oxidized group is the minimal requirement for mitogenic activity. The oxidized group adjacent to the double bond could be a hydroperoxide, alcohol, or carbonyl group with no significant difference in activity, raising the possibility that a common intermediate is involved. Activity of the fatty acid was lost either by saturation of the hydrocarbon backbone, separation of the oxidized group from the double bond by a methylene group, or by the absence of an oxidized group. These results indicated that the autoxidation products of unsaturated fatty acids may play a role in the enhancement of tumorigenesis by high levels of dietary fat and suggested a possible mechanism of action for the active compounds. Enzyme involvement with the activation of the fatty acids has been ruled out. Further studies of the metabolic fate of the active compounds are being pursued.

Nutrition in the Etiology and Prevention of Coronary Heart Disease

Coronary heart disease still accounts for the largest number of deaths in the United States in both men and women, despite the recent decline in the death rate from this condition. More than 1.25 million heart attacks occur each year, and more than 500,000 people die as a result. High blood cholesterol is one of the three major modifiable risk factors for CHD. The principal nutritional factors associated with high blood cholesterol and the development of CHD are dietary fat, particularly saturated fat and cholesterol, and energy imbalance leading to obesity. Other dietary constituents, such as fiber and alcohol, may interact with these factors in ways that are not yet clearly understood. A variety of research activities are underway to refine the understanding of nutritional factors in the development of CHD and to improve intervention strategies to reduce blood lipids and the risk of CHD and other cardiovascular diseases.

- Coronary Artery Risk Development in Young Adults (CARDIA)

Coronary Artery (Disease) Risk Development (in Young) Adults (CARDIA), is a study of the distribution and evolution of risk factors for CVD in a sample of 18- to 30-year-old black and white males and females with a range of attained education. CARDIA is designed to increase understanding of contributors to changes in CVD risk factors during the critical years of transition from adolescence through young adulthood to middle age.

CARDIA originated from the recommendations of a working group on heart disease epidemiology in 1978. A review of available literature at that time indicated that multiple studies had been conducted in middle-aged and young subjects, but that few studies had looked at the 18- to 40-year-old age group. Because young adulthood is a time in which major changes in cardiovascular disease risk factors occur, a high priority was given to initiation of studies in this age group. Because even less was known about risk factor changes in females and blacks and in Americans of different socioeconomic strata, the study was designed to enable an analysis of data comparing risk factor and lifestyle differences among these subgroups.

CARDIA was funded initially in 1983 for a 5-year cycle that included two rounds of examinations. Four clinical centers were selected. The initial examination series was successful, with 5,115 black and white participants recruited. Adequate numbers from the desired age, sex, race, and educational groups were recruited so that the planned comparisons among subgroups could be made. A second CARDIA examination was completed

1987-88. Over 90 percent of the original cohort was examined. A third CARDIA examination was completed in May 1991. The projected retention rate is 80 percent of the surviving cohort. (There have been 32 deaths.) This examination includes many of the same core measurements as past examinations, including blood pressure, lipids, anthropomorphic measurements, smoking, physical activity, and measurement of sociodemographic and other psychosocial characteristics. It also includes several new measurements: Echocardiography is being conducted in the full cohort, and 24-hour ambulatory blood pressure measurement, vascular distensibility, bioelectric impedance, and 72-hour urine collections for sodium, potassium, creatinine, and magnesium are being conducted in samples of the cohort. Planning for the fourth examination in 1992-93 is underway.

- Atherosclerosis Risk in Communities (ARIC)

Atherosclerosis Risk in Communities is a large-scale, long-term program that will measure associations of established and suspected CHD risk factors with both atherosclerosis and new CHD events in men and women from four diverse communities. The project has two components: community surveillance and repeated examinations of a representative cohort of men and women in each community. The community surveillance involves abstracting hospital records and death certificates and investigating out-of-hospital deaths. The representative cohorts include 4,000 persons from each community. Three of these reflect the ethnic composition of the communities in which they live; one cohort is black.

All cohort participants will be examined twice during the initial year contract period (1987-90 and 1990-93) and contacted annually to update their medical histories. Atherosclerosis is measured by carotid and popliteal ultrasonography. Risk factors studied include: blood lipids, lipoprotein cholesterols, and apolipoproteins; plasma hemostatic factors; blood chemistries and hematology; sitting, supine, and standing blood pressures; anthropometry; fasting blood glucose and insulin levels; ECG findings; cigarette and alcohol use; physical activity levels; dietary aspects; and family history.

The diverse communities can be compared with respect to CHD incidence and medical care and, through the cohort component, with respect to risk factors and peripheral atherosclerosis. The results will provide a measure of the variation in the distribution and determinants of CHD in the United States and, within the limits of ecologic analysis, suggest possible reasons for observed differences. The information will allow comparison with the other countries in the WHO MONICA project.

At the first examination 15,803 persons were seen. Second 3-year return rates remain high (95 percent for whites and 85 percent for blacks) with approximately 99 percent completion of annual followup calls. Community surveillance currently provides complete age-, race-, and sex-specific rates of hospitalization for myocardial infarction and coronary heart disease death in the communities for the first two years of coverage (1987-88).

- Strong Heart Study: Cardiovascular Disease in American Indians

The Strong Heart Study was initiated to estimate the morbidity and mortality rates from cardiovascular disease in three geographically diverse groups of American Indians and to estimate the levels of cardiovascular disease risk factors through an examination of 1,500 adult men and women ages 45-74 years in each of the three centers. The three centers include the Aberdeen Area Indian Health Service studying the Oglala Sioux, the Cheyenne River Sioux, and the Devils Lake Sioux in North and South Dakota; the University of Oklahoma studying the Apache, Fort Sill Apache, Kiowa, Comanche, Wichita, Delaware, and Caddo in Southwestern Oklahoma; and the Medlantic Research Foundation studying the Pima and Maricopa near Phoenix, Arizona.

Examinations have been completed on over 3,100 men and women and are scheduled to end in November, 1991. Preliminary data analyses indicate significant differences in smoking, blood cholesterol, blood pressure, obesity, diabetes, fibrinogen levels, and heart disease among the three centers.

- Hypertension and Diet

A number of studies are underway involving humans and animals in which dietary minerals (e.g., sodium, potassium, calcium) are manipulated. This form of nutritional intervention is employed to either prevent or promote the onset of hypertension or the deleterious physiological effects of hypertension. The emphasis in these studies is the elucidation of the underlying biological mechanisms involved.

- Dietary Intervention in Children with Elevated Low Density Lipoproteins (DISC)

The primary objectives of the Dietary Intervention Study in Children (DISC) are to assess the feasibility, acceptability, efficacy, and safety of long-term diet intervention in healthy prepubescent children, ages 8-10 years at entry, with elevated LDL-cholesterol levels. Participants will be randomized to either a usual care (control) group or to an intervention group who will participate in dietary intervention involving the child and the family. The full-scale trial began on December 1, 1988. DISC completed enrollment of 663 children into the full-scale trial on July 20, 1990. These children and their families will be followed for at least 36 months.

- Studies of Children's Activity and Nutrition (SCAN)

The objective of the 5-year grant program, Studies of Children's Activity and Nutrition (SCAN), (1985-1990) is to support longitudinal research studies that track the acquisition of food intake and physical activity patterns related to cardiovascular health in children who are 3 or 4 years of age at time of entry into the study. Children of families with high risk for CHD or stroke will be compared with children from families with low risk for these diseases. Several risk factors, including obesity and high blood pressure, are used for categorizing the at-risk versus the not-at-risk. Five of the studies include a significant proportion of black or Hispanic children. The multidisciplinary teams have shared measurement protocols and results of pilot studies.

- Models for Treating High Blood Cholesterol

The primary objective of the 5-year grant program, Assisting Primary-care Providers with Lipid-lowering Intervention (APPLI) is to develop and evaluate primary care models for implementing the Adult Treatment Panel Guidelines (ATP) of the National Cholesterol Education Program for detection, evaluation, and treatment of patients with high blood cholesterol. Diet therapy is considered the cornerstone of treatment. Further, the program is evaluating the feasibility and impact of applying the ATP guidelines in usual clinical practice.

Four studies comprise the APPLI program. The cholesterol management models under development utilize office systems approaches and counseling approaches. They address the needs of different medical specialties in a variety of urban and rural practice settings, as well as the needs of patients in low socioeconomic and minority groups. Several innovations in dietary management are being evaluated, including nutrition counseling via mail, simplified nutrition assessment tools for use by nonnutritionists, literacy-independent instructional tools, and the potential role of a community nutrition referral center. All four studies follow a randomized-control design and have begun the intervention phase; results are expected in 1993.

Nutrition in the Etiology and Prevention of Cancer

Indirect evidence that diet and nutrition are related to cancer risk is substantial. Dietary exposures currently being assessed include consumption of specific food groups and food items, such as meat, fruits and vegetables, ethnic dishes, and coffee; macronutrient and micronutrient intake such as fat, vitamin A, carotenoids, vitamin C, folacin, and trace elements; general nutritional status; anthropometry; biomedical indices, such as serum cholesterol and serum beta-carotene; and storage and cooking practices. Cancers studied include those of the colon and rectum, breast, lung, cervix, vulva, prostate, and oral cavity.

- Colon and Rectum Cancer

During the past year, a case-control study of colorectal cancer was completed in three Washington, D.C. hospitals. Cases and controls were interviewed regarding dietary practices. Stool samples were tested for fecal mutagenicity and for concentrations of the specific family of fecal mutagens called fecapentaenes. Results thus far indicate that more patients with colorectal cancer excreted fecal mutagens that were not members of the fecapentaene class as compared to the controls. These patients were also more likely than the control population to eat well-done meat. These two findings support a role for cooked meat ingestion as a risk factor for colorectal cancer, because carcinogenic and mutagenic heterocyclic amines are known to be produced by the cooking of meats, particularly when they are well-done.

A population-based case-control study of colorectal cancer among Chinese men and women living in California, British Columbia, and two provinces in the People's Republic of China was recently completed. Age-adjusted colon cancer rates among Chinese-American men were three times those of men in China, and they were comparable to those of U.S. whites; rates for Chinese-American females were double those in China but lower than those of U.S. white females. A similar but less pronounced pattern was seen for rectal cancer among men. By contrast, rectal cancer rates among women varied little, regardless of study area. In multivariate analysis, colorectal cancer risk was significantly associated with saturated fat intake; no relationships were seen with food energy from other sources. Colon cancer risk was elevated among men employed in sedentary occupations. Risks for cancers of both colon and rectum rose with increasing time spent sitting, on both continents and among both sexes. Further, the association between colorectal cancer risk and saturated fat was stronger among the sedentary than the active; risk among sedentary Chinese-Americans of either sex increased more than fourfold from lowest to highest categories of saturated fat intake. These observations suggest that colorectal cancer risk increases with duration of exposure to a sedentary lifestyle rich in dietary saturated fat, that higher risk among Chinese-American men relative to women is due to their longer exposure to these habits, and that a higher risk among Chinese-Americans of both sexes relative to risk in China is due to differences in such habits.

Other dietary constituents are also of interest. Higher levels of dietary calcium have been associated with decreased colon cancer risk and may act by forming calcium soaps to neutralize the effect of bowel-irritating bile acids and fatty acids. A population-based case-control study in Utah recently reported a protective effect for dietary calcium. The magnitude of the protective effect increased after adjustment for intake of calories, protein, and fat. Analysis of sera from volunteers in Washington County, Maryland, suggest a protective effect of 25-hydroxyvitamin D. These findings are consistent with an earlier hypothesis that exposure to sunlight and its associated effect on vitamin D levels may influence the observed north-south geographic gradient in colon cancer mortality in the United States.

Other studies are focusing on prevention of colon cancer and involve subjects at high risk for the development of colon cancer because of a previous colon adenoma, a lesion generally agreed to be a precursor for colon carcinoma. In another trial, researchers are studying the role of dietary fiber and calcium in subjects at risk of developing colon carcinoma by virtue of having had one or more colon polyps removed. Subjects will receive daily wheat bran fiber and/or calcium or a placebo. The primary endpoints of the study are the measurement of changes in several biochemical and/or biological markers that may reflect the risk of polyp recurrence and the compliance and tolerance to the proposed intervention. This trial will lay the foundation for a larger-scale trial to determine the efficacy of these agents in lowering polyp recurrence rates.

- Breast Cancer

Two large case-control studies of breast cancer with dietary, biochemical, and anthropometric components are being conducted in the United States. The first focuses on women of Chinese, Japanese, and Filipino ancestry living in California and Hawaii. Dietary and lifestyle patterns during childhood, adolescence, and adult life were assessed to evaluate susceptibility at different ages. On the basis of historical data, preliminary analyses indicate that breast cancer incidence among first-generation Asian migrants to the United States is higher than anticipated. This finding suggests either rapid acculturation and an immediate change in risk, or an elevated baseline risk among those Asian women migrating to the United States.

A second case-control study of breast cancer is being conducted in Buffalo, New York to evaluate nutrient associations with risk. Blood specimens taken before diagnostic biopsies and three to four months after diagnosis have been analyzed for carotenoids, tocopherols, retinol, triglycerides, cholesterol, and selenium. Results thus far indicate that cases have a lower plasma level of beta-carotene when compared with controls. Plasma alpha-carotene, lycopene, and alpha- and gamma-tocopherol were not associated with risk. Retinol was also not associated with risk, except in combination with a low level of beta-carotene. Estimated dietary intakes of preformed and precursor vitamin A were not associated with risk of disease, and there were no correlations between dietary and blood estimates of nutrients.

Relative weight and height each have been reported to influence breast cancer risk. These factors and subsequent breast cancer risk were examined among 115,534 women 30-55 years of age and free from cancer in 1976. By 1984, 658 premenopausal and 420 postmenopausal breast cancers were documented. Among premenopausal women, risk of breast cancer decreased significantly with increasing relative weight. A similar inverse association was seen for recalled relative weight at 18 years of age. Postmenopausal breast cancer was not associated with relative weight, either recent or at age 18. Height was not associated with breast cancer risk among premenopausal women and only weakly related among postmenopausal women. These data suggest that obesity among premenopausal and early postmenopausal women does not increase breast cancer risk substantially.

- Cervical Cancer

In a large case-control study of invasive cervical cancer conducted in five communities in the United States, women in the highest quartiles of intake of carotenoids, vitamin A, vitamin C, and folacin had adjusted relative risks comparable to women in the lowest quartiles, although their intake of each micronutrient was estimated to be three to four times as high. Similar results were observed in relation to *in situ* disease. Blood nutrient levels in cases and controls are now being investigated. These negative findings do not agree with studies in the published literature and suggest that the role of dietary factors in cervical cancer is not yet resolved.

- Vulvar Cancer

In a case-control study of vulvar cancer conducted in two communities in the United States, intake of carotenoids, vitamin A, vitamin C, and folacin was again unrelated to risk. However, there was a reduction in risk with high consumption of dark yellow-orange vegetables and of alpha-carotene, which is concentrated in this vegetable subgroup. This analysis was one of the first to utilize recently available data on the levels of individual carotenoids in the common vegetables and fruits.

- Prostate Cancer

Using the followup of the first NHANES cohort, studies were conducted to evaluate the effects of serum vitamin A levels. Prostate cancer risk increased as serum vitamin A decreased, with the men in the lowest quartile at 2.2 times the risk of men in the highest quartile. Because the elevated risk did not diminish with increasing time between blood draw and diagnosis, metabolic effects of early prostatic disease are not a likely explanation. The relationship of serum vitamin A to other cancers is now being investigated in this cohort.

- Oral and Pharyngeal Cancer

Analyses of data continued from the largest investigation of oral and pharyngeal cancer, a case-control study involving nearly 1,200 cancer patients in Atlanta, New Jersey, Los Angeles, and the San Francisco area. Significant protective effects were associated with high fruit intake, with those in the highest quartile of consumption having nearly half the risk of those in the lowest. The association was found in both blacks and whites, although lower intake of fruit and vegetables appeared to contribute to the higher risks of these cancers among blacks.

- Lung Cancer

Chronic obstructive pulmonary disease is another nonmalignant condition that interests cancer epidemiologists because lung cancer risk is elevated in those so affected and in their close relatives. Several hazardous exposures, such as cigarette smoking, increase the risk of both diseases; impaired pulmonary function may increase the effective time that carcinogenic agents remain in contact with respiratory tissues. The relationship of serum retinol and carotenoids to airways obstruction has been reported following a population-based study. Respiratory symptoms and pulmonary function of 83 white males were assessed five years after their blood had been drawn. Airways obstruction in 1979, defined as a forced expiratory volume in one second which was equal to or less than 75 percent of the forced vital capacity, was associated with a decreased level of serum retinol in 1974.

In both the population cited above and in a multiethnic population in Hawaii, serum beta-carotene levels showed a strong protective effect for lung cancer. In Hawaii, a clear dose-dependent negative association was demonstrated between dietary beta-carotene and lung cancer risk in both sexes after adjusting for smoking and other covariates. The relationship was stronger for women. All vegetables, dark green vegetables, cruciferous vegetables, and tomatoes showed stronger inverse associations with risk than did beta-carotene. This observation suggests that other constituents of vegetables, such as lutein, lycopene, and indoles, may also protect against lung cancer in humans.

- Heterocyclic Amines and Cancer

It has now been thoroughly documented that during normal cooking practices using beef, fish, and other meat products, a number of heterocyclic amines are formed. Following their consumption, these compounds or their metabolites have been detected in human body fluids. Although their potential role in the etiology of human cancer is at present unclear, several of the heterocyclic amines have now been found to be carcinogenic in rodent bioassays, inducing tumors of the liver, forestomach, and intestine. One of the heterocyclic amines, known as PhIP (2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine), is the compound that is present in highest concentration in cooked beef and has been shown to induce breast and colon cancer in rodents and to produce DNA adducts in nonhuman primates. The current methodology for detection of these compounds, both in their parent state or as metabolites, is well established. NCI is currently involved in an extensive research program focused on the metabolism, genotoxicity, and carcinogenicity of these food-derived heterocyclic amines in both rodent and nonhuman primate experimental animals. Research on the mechanism of action of this class of mutagens and their interaction with cellular DNA will be expanded, as will studies to evaluate the potential role these chemicals may play in the etiology of human cancer. Studies continue on improvement in risk extrapolation to humans and on methodology to limit the formation of these heterocyclic amines in cooked meat.

Osteoporosis

The prevalence, health consequences, and expense of osteoporosis among Americans, especially among older women, make it a compelling public health priority. The principal dietary factors related to osteoporosis are calcium, phosphate, and vitamin D (and its hormonally active form, calcitriol). How these factors affect peak bone mass development requires further elucidation. In postmenopausal women, estrogen-replacement therapy is the best documented method of preventing osteoporosis, but other lifestyle factors, such as increased exercise and decreased cigarette smoking may also decrease bone loss. The dietary factors associated with bone mass, the universality of bone loss with age, the interaction of diet and lifestyle with genetic factors, and the difficulties in measuring bone loss in populations make defining the relationship between diet and osteoporosis difficult. Nonetheless, this remains an active area of research.

- Intestinal Absorption and Bioavailability of Calcium

Alterations in calcium absorption contribute to abnormal mineral metabolism in metabolic bone disease. The management of patients with these disorders would be improved if clinically useful measures of calcium absorption were available. Calcium absorption can be quantitated by the balance method or by double isotope techniques. True fractional calcium absorption, assessed by the balance method, is based on the proportion of the dietary calcium intake measured in total stool collections, with appropriate corrections for recovery and endogenous stool calcium. Although this method is highly accurate, it is very labor intensive and requires admission of patients to a metabolic unit for one to two weeks. Absorption also can be measured by labeling dietary calcium with ^{47}Ca and then injecting ^{45}Ca intravenously. Fractional absorption is the quotient of the two tracers in samples of pool calcium relative to the administered dose. This is usually followed by making measurements of serum and urine calcium radioactivity over several days to achieve an equilibrium value. Although both of these methods have proven useful for clinical research, they have not been generally applicable to patient management. The balance method is very time consuming, and the use of the isotopic method is limited because of radiation exposure concerns.

A recent, long-term study using both the balance and isotopic techniques has confirmed that calcium absorption is inversely related to calcium intake and, moreover, is dependent on estrogen status and age. This study followed a cohort of women for 17 years, making multiple measurements of calcium absorption on each woman, providing information about the degree of individual variation in calcium absorption in a free-living white female population.

A new and potentially useful measure of calcium absorption in patients may provide an economically and technically feasible method to identify individual low- and high-calcium absorbers. This method uses stable isotopes of calcium administered with the subject's usual diet and then measured by mass spectrometry in a 24-hour urine collection. The true fractional calcium absorption calculated from stable isotope absorption correlated well with a 7-day balance study. The advantages of this new method are avoiding exposure to radioisotopes (permitting extension of balance studies to pregnant women and children), improving precision, and lowering cost compared to radioisotope methods. Currently, the limited availability of the mass spectrometry may limit its utilization.

Interindividual variation in calcium absorption appears to account for most of the variability observed in healthy volunteers. Future research will focus on the factors responsible for this variability, but it now seems possible to begin to apply new methodology to patients with metabolic bone disease or those at high risk. Modifying dietary calcium intake or prescribing calcium supplements can begin to have a more rational basis.

There is general agreement that the best natural source of calcium is dairy products, where the bioavailability--the amount of calcium absorbed and used by the body--is established. Scientists recently have measured the absorption of calcium from kale. In contrast to the poor absorption of calcium previously reported from spinach, kale, a low oxalate vegetable, exhibits excellent calcium absorbability--in fact, slightly better than milk.

- Fluoride Effects on Bone

The ideal therapy for osteoporosis would restore lost bone and correct alterations in architecture that contribute to fractures. Current treatments, such as estrogen and calcitonin, only prevent further bone loss. Several studies have indicated that sodium fluoride can contribute to the restoration of bone mass, and it has been used extensively in Europe to treat osteoporosis. Until recently, there had been no well-controlled clinical trials of the effects of fluoride in women with post-menopausal osteoporosis using fracture frequency as an end point. The results of two such placebo-controlled, double-blind studies confirmed that sodium fluoride supplementation (75 mg/day) increased bone mass.

However, both studies failed to establish any efficacy of fluoride in fracture reduction. In spite of these disappointing results, fluoride does have the capacity to induce bone formation. Further investigation of the basic mechanism of fluoride action on bone is clearly warranted. Some possibilities for future clinical investigations include trials with different formulations and dosages of fluoride, as well as a study of whether the addition of fluoride to standard antiresorption regimens can be beneficial.

- Vitamin D and Bone

The active metabolite of vitamin D_3, 1,25-dihydroxyvitamin D_3, is highly effective in regulating the absorption of calcium from the intestine and has a strong influence on the metabolism of bone cells. The receptors for this active agent are intracellular polypeptides. The human vitamin D receptor has recently been cloned and sequenced. The full nucleotide sequence shows similarity with other steroid hormone receptors and thyroid hormone receptors. These studies support a hypothesis that the mechanism of vitamin D action involves interaction of the receptor-bound active agent with nucleotide sequences in the nucleus of the target cells, paralleling the action of steroid hormone receptors. Advances in the cloning and sequencing of the human vitamin D receptor provide an opportunity for enhanced functional studies of vitamin D activity in target cells.

- Regulation of Calcium-binding Protein

Calcium-binding protein is involved in active intestinal calcium transport. The regulation of the calcium-binding protein, calbindin-D, in the intestine has been largely unknown, although it has been thought that its expression can be mediated by 1,25-dihydroxyvitamin D_3. Recent studies have demonstrated that the use of side-chain-modified analogues of 1,25-dihydroxyvitamin D_3 caused greater than a sevenfold increase in calbindin-D 9k mRNA without stimulating intestinal calcium transport. In contrast, 1,25-dihydroxyvitamin D_3 caused a parallel increase in both calbindin-D 9k mRNA and intestinal absorption of calcium. Thus, these data suggested that calbindin-D 9k is not by itself responsible for the 1,25-dihydroxyvitamin D_3 mediated increase in intestinal absorption of calcium.

The influence of vitamin D status, serum calcium, and serum phosphorus levels on 1,25-dihydroxyvitamin D_3 receptor levels in the kidney were investigated in weanling rats. It was shown that in the absence of vitamin D, total receptor concentration was increased twofold by an increase in serum calcium concentration. At normal serum calcium levels, the administration of vitamin D resulted in a fivefold increase in receptor concentration. However, in hypocalcemic animals, vitamin D did not change receptor levels. There was no association between serum phosphorus levels and changes in the 1,25-dihydroxyvitamin D_3 receptor concentration.

The 1,25-dihydroxyvitamin D_3 is believed to mediate the regulation of calcium metabolism by a steroid hormone receptor mechanism. Investigators have now demonstrated that phosphorylation of the 1,25-dihydroxyvitamin D_3 receptor occurs rapidly in embryonic chick duodenum organ culture in response to 1,25-dihydroxyvitamin D_3. Phosphorylation occurs in this system prior to the initiation of calcium uptake or induction of calcium-binding protein. This chick duodenum organ culture system is vitamin D-responsive and closely parallels *in vivo* rachitic chick intestine. The occurrence of receptor phosphorylation in this system in response to 1,25-dihydroxyvitamin D_3 strongly suggests that it is a physiologically relevant event, and thus, it appears possible that phosphorylation may play a significant role in the 1,25-dihydroxyvitamin D_3 regulation of transcription in the intestine.

- The Roles of Growth Factors, Vitamin D, and the PTH-like Proteins in the Regulation of Bone Metabolism

The interaction between factors that stimulate bone formation and bone resorption represents a major determinant both of serum levels of minerals, and skeletal integrity. In this regard, parathyroid hormone (PTH), plays a key role in normal bone and mineral homeostasis. The recent discovery that there is a PTH-like peptide that is released in certain malignancies has served to focus attention on the mechanism of action of PTH and related peptides in bone and mineral metabolism. A number of other hormones also regulate bone metabolism, including vitamin D, estrogen, and other steroid hormones. Although receptors for many of these hormones have been identified on bone, the precise mechanisms by which they influence bone metabolism are unknown. A number of local growth factors and cytokines have been identified that may mediate the effects of systemic hormones on bone. Finally, much recent evidence has pointed toward the presence of a number of bone-specific proteins which are the targets of bone-active hormones and growth factors.

A variety of human solid tumors produce a polypeptide with close homology to PTH. This PTH-like protein binds to the PTH receptor, reproduces the major biologic effects of PTH, and is responsible for the humorally mediated hypercalcemia associated with cancer. The finding of circulating PTH-like protein in normal subjects suggests it may play a normal physiological role. Levels of PTH-like protein in milk are 10,000-fold higher than the circulating plasma concentrations in normal subjects. The local function of PTH-like protein in mammary tissue remains to be determined. It may play an important role in calcium metabolism and milk production. It also may modulate gastrointestinal calcium absorption during suckling. Levels of this protein are lower in milk-based infant formulas than in unprocessed milk, and are absent in soy-based formulas. PTH-like protein may be one factor responsible for the differences in calcium homeostasis between breastfed and formula-fed infants.

The amount of bone present represents the net difference between the processes of bone formation and resorption. The cells that carry out these processes are regulated by a number of hormones and growth factors. Recent work has indicated that one such growth factor, insulin-like growth factor I (IGF-I), is made by osteoblasts in response to hormones that stimulate bone formation. Bone cells also make the necessary binding proteins and receptors that allow them to respond to IGF-I. The mechanism of action of IGF-I on these cells is at least partly by stimulation of bone cell replication and the synthesis and release of collagen by these cells. Moreover, certain pathological conditions, such as steroid-induced osteoporosis, may affect bone by altering the ability of bone cells to make IGF-I, thus accounting for the inhibitory action of glucocorticoids on bone formation. Finally, the PTH-like protein found in certain malignancies, a factor that accounts for hypercalcemia of malignancy (also known as parathyroid hormone related peptide or PTHrp), has been found to also inhibit local production in bone of IGF-I. Thus, a common point of action for the regulation of bone formation appears to be localized to the regulation of bone cell IGF-I production.

In addition, there are a series of bone-specific proteins that have been discovered and only recently understood. One such protein is osteocalcin (G1a). Expression of the gene for this bone-specific protein has been implicated in bone formation. Expression of this gene is directly regulated by $1,25(OH)_2D_3$ (the active form of vitamin D). The gene has been cloned and sequenced and the 5' flanking region identified. Detailed molecular analysis of this region of the osteocalcin gene has now revealed that there are at least two domains which contribute to responsiveness to vitamin D, with only the region closest to the promoter able to specifically confer responsiveness. These sites are similar to those described for steroid hormone response elements, such as those for estrogen, and mediate both binding of the vitamin D receptor and transcriptional activation of the osteocalcin gene.

The recent advances in understanding of a variety of hormones and growth factors that regulate bone and mineral metabolism has opened the door to study the roles of these factors in the normal and pathological homeostasis of body bone and mineral content. Clearly, the discovery of the PTH-like protein in pathological conditions suggested that it may simply represent the inappropriate expression of a normal bone-active hormone. The discovery of its presence in mammalian milk, together with the discovery that it may have a distinct role in bone metabolism, suggest that it is indeed a normal component of the overall mix of factors influencing bone and mineral metabolism, perhaps most important during early development. Factors such as PTH-like protein may also interact with IGFs at particular times to modulate overall bone resorption. Indeed, it may be that the net response of dynamic tissues, such as bone, to changing physiological conditions involves the interplay of numerous hormones and growth factors. Finally, the ultimate target of these factors is often a tissue-specific protein, such as osteocalcin. Understanding the molecular mechanism of hormone action on such proteins greatly furthers our understanding of both normal and pathological changes in tissues such as bone.

- Nutrition and Bone Health in Older Women

In a recent prospective study, elderly women were found to still lose approximately 1 percent of their bone mass per year despite a calcium intake of over 900 mg/day. The reasons for the observed high rate of bone mass loss have not been satisfactorily established, but the rate of loss relates to several factors, including a decline in efficiency of intestinal absorption with age, a marked fall in circulating estrogens, and a decline in renal function. Perhaps more importantly, a diminution in lean body mass, indirectly linked to restricted physical activity, may also play a predominant role.

- Calcium Transport to the Developing Chick Embryo

Calcium is a major nutritional requirement for vertebrate embryonic development, required for physiological functions, such as skeleton formation, neuromuscular activity, and blood coagulation. In avian species, the chorioallantoic membrane transports calcium from the eggshell to the developing embryo, and it can be used as a simple experimental model for the study of transplacental calcium transport.

Several components of the chick calcium transport system have been identified. A specific calcium-binding protein, localized on the surface of calcium-transporting ectodermal cells of the chorioallantoic membrane, functions as a calcium receptor. It is activated by an enzymatic reaction that is dependent on vitamin K. The calcium is incorporated into a vesicle inside the cell, from which it is eventually released by a mechanism that involves acidification of the vesicle. Near the receptor on the cell surface is a calcium-activated ATPase that somehow functions intracellularly to maintain the vesicular calcium load.

Nutrition in Maternal and Child Health

Several of the *Healthy People 2000* nutrition objectives address issues related to the health of mothers and children. For example, women and young children represent groups at risk for iron deficiency. Women of childbearing age are at increased risk for iron deficiency because of iron loss in menstruation and because of the iron requirements of pregnancy. Maternal iron deficiency during pregnancy and lactation increases the likelihood that the infant will be iron deficient in the early years of life. Chronic iron deficiency in childhood may have adverse effects on growth and development. Retardation in linear growth in preschool children serves as an indicator of overall health and development and may reflect the interaction of a variety of factors but may especially reflect the adequacy of a child's diet. Inadequate maternal weight gain during pregnancy and other prenatal factors that influence birth weight also affect the prevalence of growth retardation among infants and young children.

The emphasis given to the promotion of breastfeeding recognizes that it is the optimal way of nurturing full-term infants while simultaneously benefitting the lactating mother. Research is underway at NIH to test the effectiveness of interventions designed to promote and assist breastfeeding among subgroups of women who are likely to choose not to breastfeed or to breastfeed with limited success. Efforts are also being made to determine the relative stress of breastfeeding versus bottle feeding for preterm infants, as measured by coordination of sucking, swallowing, breathing, transcutaneous oxygen pressure, transcutaneous carbon dioxide pressure, oxygen saturation, body temperature, heart rate, duration of feeding session, and volume of intake. Examples of other nutrition research findings affecting maternal and child health are provided in the following section.

- New Gastric Delivery System (GDS) for Iron Supplementation

It is estimated that, globally, more than 50 percent of pregnant women develop anemia during pregnancy due to a lack of iron. There has been heightened awareness in recent years of the liabilities associated with even mild iron deficiency anemia during pregnancy. The major consequences include premature delivery, low birth weight, and a higher rate of obstetrical complications. Appreciation of the health consequences of anemia during pregnancy is the outgrowth of basic science investigations, that have led to the development of newer and more sensitive laboratory methods, such as measurement of serum ferritin and transferrin-binding protein to detect and quantify iron deficiency during pregnancy.

Despite expanding knowledge about the consequences of anemia during pregnancy, progress in developing methods to alleviate it has been at a standstill for decades. International donor agencies, such as UNICEF, supply nearly 1 billion iron tablets annually for distribution to pregnant women in primary health care centers in developing countries, but there is no evidence that these iron supplementation programs have had any impact on the prevalence of iron deficiency. One of the main reasons is poor compliance due either to the gastrointestinal side effects associated with iron therapy, such as nausea, vomiting, loss of appetite, and stomach discomfort, or simply the need to take several tablets daily over a long period. There are several slow release pharmaceutical preparations marketed at the present time which reduce gastrointestinal symptoms. However, the absorption of iron from these is sharply reduced and their cost is prohibitive.

Researchers have recently reported the development of a new gastric delivery system (GDS) for iron supplementation in tablet form. The GDS delays the release of iron, utilizing altered hydrodynamic properties that impact the dissolution rates. This allows a gradual release of ferrous sulfate into gastric secretions and results in maximal absorption of iron. The new GDS was achieved in collaboration with a pharmaceutical company by incorporating iron into a mixture of food extracts that render it buoyant on exposure to gastric secretions. Because the preparation floats on the surface of the gastric secretions, it is retained in the stomach. Iron is gradually released at the surface of the preparation over a period of three to four hours. Selection of the optimal combination of ingredients for GDS was made possible by performing radioisotopic measurements of iron absorption in human volunteer subjects. These sophisticated measurements have been developed and refined over the past many years in laboratories supported by the National Institutes of Health. Without these accurate clinical measurements of iron absorption, the time and cost in developing GDS would have been prohibitive.

An extensive field trial in over 400 pregnant women living in Kingston, Jamaica, was just concluded. Preliminary findings indicate that the hematological response of one GDS tablet daily for three months is at least equal to two tablets of conventional iron given daily.

GDS should have a major impact on the global prevalence of iron deficiency during pregnancy. Because iron is infused slowly over several hours at a high level of the gastrointestinal tract, iron absorption is two- to threefold higher than with conventional iron preparations. Thus, administration can be reduced to once daily, while retaining comparable efficacy. More important, double-blind placebo controlled trials have demonstrated that the gastrointestinal side effects of iron therapy are eliminated with GDS. These two major advantages will result in improved participation in iron supplementation programs and a consequent reduction in anemia prevalence.

- Nutritional Effects on Reproduction

The mechanisms by which nutrition modulates reproductive neuroendocrine function is not understood. The investigators have developed a model, a nutritionally restricted, growth-retarded lamb, which is sensitive to alterations in diet, and have used it to explore the interfaces between nutrition and reproduction. Limited nutrition in the ovariectomized lamb results in an impairment of LH and FSH secretion, a phenomenon that is rapidly reversible by increasing the level of nutrition and is independent of ovarian steroid feedback. An increase in the level of nutrition produces profound changes in the synthesis, storage, and secretion of LH, FSH, and GH (growth hormones). The concentrations of gonadotropin subunit mRNAs (i.e., LH beta and FSH beta) were significantly higher in response to increased nutrition. These studies show that pituitary biosynthetic events, as well as secretory processes, can be changed markedly by the level of nutrition.

In related studies, the investigators explored the hypothesis that both GnRH and the steroid milieu alter the quantity, as well as the quality, of the secreted or circulating gonadotropins. The quality of the hormones has been determined by differential post-receptor binding events defined as bioactivity and compared to immunoreactive measurements with further confirmation of isoform pattern changes by chromatofocusing. Studies during puberty have shown significant increases in B-LH (bioactive) with each stage of sexual maturation which significantly exceed I-LH (immunoactive) concentrations, but no significant change in B-FSH levels. The only time when B-LH levels rise significantly is during the periovulatory period in cycling women. The investigators conclude that a constant presence of B-FSH may be required for the maintenance of growth and function of the gonads with an increase in B-FSH for ovulation. These studies contribute to our understanding of the factors that affect the quality and quantity of gonadotropin secretions during reproductive events and processes.

- High Risk Pregnancy

A recognized high-risk group for poor pregnancy outcome is that of adolescent gravidas. A cohort of 1,790 teenage gravidas were studied to determine their weight during pregnancies and its relationship to fetal outcome. This question is of particular importance, as low prepregnant body mass is more common in this age group than at maturity. Low-income teenage gravidas are likely to have poor nutritional status and poor diets during pregnancy and may intentionally limit early weight gain because of body image concerns. This study shows that early inadequate weight gain poses an increased risk of having a small-for-gestational-age infant, even when later gains brings the total weight gain to within accepted standards. Late pregnancy inadequate gains are associated with preterm delivery whether or not the total gain is adequate for gestation. These results suggest that prenatal care protocols for adolescents that do not focus on balanced weight gain throughout gestation may reduce preterm delivery, but may not affect the incidence of intrauterine growth retardation.

A prospective longitudinal evaluation of change in body composition and energy expenditure in nonobese healthy women during pregnancy has shown that by 12-14 weeks gestation there is a 24 percent increase in body fat which accounts for 72 percent of early weight gain. At the same time, there is a 14 percent increase in basal oxygen consumption, which represents 58 percent of the total increase in basal energy expenditure through late third trimester. These findings suggest that much of the metabolic adaptation to gestation occurs in early pregnancy.

- Beneficial Effects of Human Milk

To investigate the role of breastfeeding in preventing diarrhea caused by *Campylobacter jejuni*, 98 Mexican children were followed prospectively for 2 years beginning at their birth. Attack rates of diarrhea in children less than 6 months of age who were not fed human milk were 2.3 times greater than those in children of the same age who were fed human milk. Breastfed children remained free of diarrhea for a longer time than nonbreastfed children. The diarrhea attack rate caused by *C. jejuni* for nonbreastfed infants was significantly greater than that in the breastfed group. Secretory IgA milk antibody titers against glycine acid-extractable antigen of *C. jejuni* were high in colostrum, decreased during the first month of breastfeeding, and generally persisted throughout lactation. Human milk consumed by children in whom campylobacter diarrhea developed did not contain secretory IgA antibodies to the glycine acid-extractable common antigen of campylobacter. This study shows an association between campylobacter antibodies in human milk and prevention of diarrhea caused by campylobacter.

In another study, human milk was found to block the binding of the outer coat protein of the human immunodeficiency virus (HIV), GP 120, to the cellular receptor for this protein, CD4, in a solid phase assay. Bovine milk did not block this binding. The activity of the protein fraction accounted for almost all of the inhibitory activity of milk. The activity was not found in the protein fractions that bound to a concanavalin A affinity column, but was found in the fraction that passed through, indicating that the active molecule was not mannosylated. The activity was partially retained by a 0.45 micrometer filter, indicating that the active constituent could be associated with large aggregates in its native state. When applied to a molecular sieving column, the activity was found in the void volume of the column, indicating that the activity was associated with a molecule or aggregate that is in excess of 300,000 daltons. The activity is stable to heat, unstable to methanol, and is partially destroyed by treatment with a commercial sulfatase preparation. After preparative isoelectric focusing, most of the activity is found in the fraction with an isoelectric point of approximately 9.0-9.5, and this fraction has three unique bands by polyacrylamide gel electrophoresis, two of which are positive for sugars by PAS stain. These results are consistent with the activity being due to a nonimmunoglobulin protein or large glycoconjugate that may be associated with the milk-fat globule membrane and may be sulfated.

Nutrition and Aging

Older persons also represent a group at risk of nutritional disorders because aging is accompanied by a variety of physiological, psychological, economic, and social changes that may compromise nutritional status. However, the ways in which the aging process affects energy balance, specific nutrient requirements, and nutritional status remain to be fully elucidated. The ways in which nutritional status might influence alterations in tissue and organ function change with age and may influence relationships between dietary components and the occurrence of chronic diseases of old age. Findings of NIH-supported investigators that address some of these research needs are reported below.

- Effects of Age-Related Changes in Riboflavin Metabolism

Riboflavin is involved with many metabolic pathways in mammalian systems. Using a riboflavin-deficient rat model, an investigator is attempting to determine whether aging alone and aging in association with modification of nutritional factors influence neurotransmitter function, antioxidative defense, free-radical formation, development of age-related diseases, and the efficacy and toxicity of certain drugs, including adriamycin, alcohol, and menadione. A number of interesting results have emerged from this research.

Lenses of deficient animals compared to controls have markedly diminished glutathione (GSH) levels, lowered basal glutathione reductase activity, and elevated glutathione reductase activity coefficients. These findings imply that riboflavin deprivation may increase the risk for cataracts in lenses of individuals receiving adriamycin for treatment of cancer.

Riboflavin plays an important role in regulating thyroid hormone, which in turn modulates the action of both beta-adrenergic agonists and adenosine. The drug adriamycin, which inhibits riboflavin metabolism, was administered to deficient and normal rats. In control rats, serum aldosterone levels were enhanced, while serum levels of T3 and T4 were significantly lowered in a dose response manner. Riboflavin-deficient animals had lower basal levels of aldosterone and markedly attenuated responses to adriamycin compared to the controls. These results suggest that the flavins play an important role in regulating the levels of aldosterone, T3, and T4 and may modify the cardiovascular toxicity associated with adriamycin therapy.

Preliminary studies indicate that both liver and erythrocytes of riboflavin-deficient rats, at all ages studied (21-91 days), had an elevation in GSH, reduction of glutathione reductase activity, and a decrease in the malondialdehyde production compared to normal controls. Additional data show that there is an increase in the activity of gamma-glutamyl cysteine synthetase in the liver of the deficient rats, which may be responsible for greater GSH concentrations in these animals.

Previous work demonstrated that marginal zinc deficiency may lower circulating vitamin E concentrations. This interaction may influence other antioxidative systems, including GSH concentration and the glutathione reductase-peroxidase system. To test this hypothesis, Sprague-Dawley rats were fed diets either high or low in vitamin E and zinc. Preliminary results show that low levels of vitamin E and zinc adversely affect liver levels of GSH and that low dietary vitamin E, regardless of dietary zinc, significantly increases lipid peroxidation in hepatocytes.

- Effects of Uninephrectomy in Young and Old Animals on Vitamin D and Bone Metabolism

Tissue factors in the kidney, such as insulin-like growth factor or epidermal growth factor, may modulate kidney hypertrophy and renal 25(OH)D 1-alpha hydroxylase after acute reduction in kidney mass. Alternately, changes associated with increased kidney mass, e.g., prostaglandin or protein kinase-C activity, may stimulate $1,25(OH)_2D$ production. Age may play a significant role in the regulation of vitamin D metabolism. Several studies have shown decrements in renal hydroxylase activity and serum $1,25(OH)_2D$. These data agree with the hypotheses that type II osteoporosis may be related to a defect in the conversion of 25(OH)D to the active $1,25(OH)_2D$ metabolite.

Investigators studied the metabolic impact of uninephrectomy on young and old mice. A distinct age-related prolonged impairment of the compensatory response of remnant kidney 25(OH)D hydroxylase activity was noted. Changes in calcitriol production were blunted and occurred more slowly in aged mice. The uncoupling of vitamin D production from total renal mass may indicate a compromise in the ability of older renal tissue to regulate vitamin D homeostasis in the face of surgical challenge.

Nutrition and Neurological Function

The designation of the 1990s as the Decade of the Brain recognizes both the tremendous opportunities presented by recent and anticipated advances in brain research and the enormous costs that disorders of the brain exact. Knowledge of interactions between nutrition and the brain and nervous system is evolving, but many issues remain unresolved. The influence of nutrition on central nervous system function in health and disease, neurotransmitter synthesis, sensory disorders, behavior and mental disorders, development of the brain, and learning and memory, as well as the role of the brain in appetite and food intake, are under investigation by NIH-supported researchers. Some selected studies of nutrition and neurological function are summarized here.

Dietary Protein and Response to L-dopa in Parkinson's Disease

Scientists are searching for insights into the effect of certain amino acids on L-dopa-treated Parkinson patients who suffer unpredictable motor fluctuations or "off" periods. Intake of protein among study subjects will be redistributed to be consumed at specified periods during the day. Drug and diet interactions will be analyzed to determine if blood and spinal fluid levels of the amino acids interfere with the sensitivity and effects of L-dopa.

Postnatal Undernutrition

The various effects of postnatal undernutrition on the nervous system are being studied using developing rats as an experimental model. Investigators are seeking to identify how starvation influences the synthesis of the myelin nerve sheath, the development of the neurotransmitter receptor binding system, and maturation of optic mechanisms.

The Effects of Aspartame

In animal studies, the widely used artificial sweetener, aspartame, is being investigated for possible effects on brain metabolism of newborns. Early results show that the animals administered the sweetening agent exhibited alterations in behavioral responses to stimuli when compared to a control group. Studies will continue to monitor for signs of teratogenicity and changes in brain metabolism.

Brain Transport and Metabolism in Hypoglycemia and Diabetes

Both diabetes and chronic hypoglycemia alter brain fuel transport in a parallel manner. In an ongoing study, researchers hope to determine whether the changes in glucose and hexose metabolism induced by diabetes impair the ability of the brain's microvessels to maintain their energy status when made anoxic *in vitro*. These studies will advance understanding of the regulation of brain hexose transport, its relation to microvascular metabolism, and the factors altering it. This research also may help to explain why diabetes reduces cerebrovascular tolerance to oxygen deprivation.

Blood Lipid Levels and Stroke

Researchers involved in the Framingham study report that there seems to be no connection between elevated blood lipid levels and increased risk of stroke. The cohort of 5,200 men and women have been followed prospectively for more than 35 years. An investigator working on the study observed that there continues to be no straightforward relationship between increasing levels of serum cholesterol and increasing incidence of stroke generally, or of brain infarction. However, cholesterol does seem to be important in the formation of carotid artery plaques which may cause stroke by artery occlusion. This points out some obvious differences between coronary atherosclerotic disease and cerebral disease.

Maternal Dietary Zinc Intake and *In Vitro* Tubulin Polymerization in Fetal Rat Brain

The hypothesis that one of the biochemical lesions underlying zinc deficiency-induced teratogenicity is altered microtubule function was tested. Day 19 fetuses from zinc-deficient Sprague-Dawley dams were characterized by low brain supernate zinc concentrations and slow brain tubulin polymerization rates compared to controls. Brain supernate tubulin and protein concentrations were similar in zinc-deficient and control fetuses. *In vitro* brain tubulin polymerization was increased following addition of zinc to either control or zinc-deficient brain supernates; however, the stimulatory effect of added zinc on polymerization was significantly higher in brain supernates obtained from zinc-deficient fetuses compared to controls. These results support the idea that one effect of fetal zinc deficiency is a reduction in tubulin polymerization, which in turn may result in altered microtubule function.

Neurological Basis of Feeding and Drinking

An effort is underway to identify and characterize neuronal mechanisms in the brain stem which affect gastric function. Emphasis will be placed on the response of the central neuronal portion of the brain stem, which receives afferent input from the stomach. Anticipated results will provide the basis for more informed decisions into diagnosis and treatment of digestive problems, including eating disorders such as obesity, anorexia, and bulimia.

Both hormonal and neural signals from the gastrointestinal tract are thought to participate in the process of satiation following the ingestion of food. Chemical and mechanical stimulation of the digestive tract release peptide hormones and activate viscerosensory neurons; however, the role of individual hormones and their interaction with particular stimuli involved in the control on ingestion is unclear. Both cholecystokinin and opiate peptides are known to be involved in the central nervous system control of feeding behavior. Current studies of these and other chemical messengers will yield increased understanding of how specific putative endocrine and neural satiety signals are relayed and processed by the nervous system.

Other animal studies are investigating hormones of renal sodium regulation to clarify whether their synergistic action in the brain stimulates excess sodium intake. Excess salt intake is implicated in the etiology of some hypertensive disease; therefore, an understanding of its hormonal causes could lead to rational chemical therapies and to reductions of salt intake in humans at risk for hypertension.

Nutritional Therapy for Adrenoleukodystrophy and Adrenomyeloneuropathy

Adrenoleukodystrophy (ALD) and adrenomyeloneuropathy (AMN) are related genetic metabolic diseases that follow an X-linked pattern of inheritance. Both are due to a peroxisomal enzyme defect, resulting in an impaired ability to oxidize very long chain saturated fatty acids (VLCFAs). The accumulation of these VLCFAs in the nervous system causes demyelination and neurologic impairment. ALD appears in childhood or adolescence with a rapidly advancing, devastating cerebral demyelination that causes dementia and death. In the milder, late onset form of AMN, demyelination of the peripheral nervous system causes spasticity and gait disorders. In both diseases, there are also various degrees of adrenal insufficiency.

Preliminary experiments indicated that the synthesis of the major VLCFA (C26:0) was decreased in cultured fibroblasts from ALD patients when the cells were grown in the presence of monounsaturated fatty acids. This effect resulted in a decrease in cellular VLCFA accumulation. Oleic acid (C18:1) was found to be effective, but erucic acid (C22:1) even more effective in these experiments. In a double-blind crossover study of ALD patients on chronic oleic acid therapy, the addition of erucic acid to the diet led to a further VLCFA reduction in the treated patients' plasma. When 12 patients with symptomatic ALD and demyelination (revealed by brain MRI) were treated with dietary erucic acid, the mean plasma C26:0 normalized within 4 weeks, and the C26:0 content of plasma sphingomyelin normalized in five patients when measured at four months. Of eight patients who were treated longer than 6 months, three mild patients stabilized clinically and five progressed. There were no adverse effects of the therapy.

An ongoing therapeutic clinical trial for ALD and AMN patients with a 4:1 mixture of glyceryl trioleate and glyceryl trierucate is showing early promise for AMN patients. In addition to these patients' lowered levels of VLCFAs, they also demonstrated improvement in peripheral nerve conductance. ALD patients who have entered the phase of rapid central nervous system deterioration show only a reduction of their VLCFA levels, without a reversal or delay in the rapid clinical progression. In order to preempt the initiation of the rapid progressive neurologic decline, the trial has been extended to asymptomatic affected boys who exhibit only elevated levels of plasma VLCFAs. Female carriers who develop late onset symptoms also will be included in the clinical trial.

Dietary therapeutic intervention with erucic acid shows promise for AMN patients and potential promise for asymptomatic boys with ALD and symptomatic female carriers. Patients with more severe forms of ALD have biochemical response to treatment without clinical improvement. It has been suggested that once the disorder has progressed to significant neurologic involvement, altered myelin may cause ongoing immunologic damage. These exciting results show promise in the mild forms of a devastating disease.

Dietary Restriction

In rodents, caloric restriction without essential nutrient deficiency has been shown to extend maximum life span, reduce the incidence of spontaneous tumors, retard the onset of many late-life diseases, and slow the rate of biological aging. The relevance of these findings to human aging is unclear. Researchers are employing this model in studies of several areas of basic biology, such as peroxidation and free radicals, intermediary metabolism, and chemical carcinogenesis. The effects of caloric restriction on energy metabolism, gene expression, neuroendocrine regulation, and immune function are under investigation. The following summaries highlight NIH-supported work in the area of dietary restriction.

Dietary Restriction in Monkeys

A study has been undertaken to determine whether a 30 percent calorie reduction in the *ad libitum* diet of rhesus and squirrel monkeys affects the aging rate of a number of physiological, biochemical, and behavioral systems, as it does in rodents. After four years of calorie restriction, reduced rates of weight gain are apparent in restricted juvenile and adult animals, as are reductions in skeletal growth in juveniles. Weight to height ratios, however, are substantially lower (up to 40 percent) in monkeys in the experimental group. Concomitant reductions in various body girth dimensions are also apparent. Longitudinal age changes have been observed for a number of parameters.

Effects of reduced feedings are now becoming apparent for at least two of these. Puberty (as indexed by a rise in plasma testosterone levels) appears to be delayed by at least a year in the calorie-restricted rhesus monkeys. In addition, decreases in serum alkaline phosphatase levels also seem to occur later in restricted animals.

The effects of caloric restriction may be different in rhesus and squirrel monkeys and possibly among different subgroups of rhesus monkeys, due to genetic variation. For example, a group of 30 rhesus monkeys that were raised in China and entered the study in 1988 have substantially lower serum cholesterol levels than the American-bred monkeys, despite the fact that both groups have been on identical dietary regimens for 3 years. In addition, no effects of caloric restriction have been observed on the age-related decrease in serum alkaline phosphatase in squirrel monkeys, even after 4 years. The addition of female monkeys to the study offers the opportunity to assess the effects of age and diet on female endocrine/reproductive status and compare the possible gender differences in responsiveness to dietary modulation of aging processes.

Dietary Restriction, Cancer, and Aging

The investigators have shown that small and large intestinal crypt hyperplasia and hyperproliferation occur in senescent rats. Caloric restriction retards these intestinal changes as well as increases the life span of the animals from 27 to more than 33 months. After weaning, male rats were calorie restricted to 60 percent of the *ad libitum* diet consumed by age- and weight-matched controls. Crypt cell population in the control rats was 61 percent more at 21 months and 83 percent more at 27 months. In the calorie restricted animals, the crypt cell population remained relatively constant up to 27 months but increased between 27 and 33 months. Because hyperproliferation is an important determinant for carcinogenesis, these studies support the hypothesis that age-associated hyperproliferation is a contributing factor in the development of colon cancer in old age. Thus, caloric restriction provides an experimental model for the study of age-related cellular changes leading to cancers and other syndromes of the aging rodent's gastrointestinal tract. In a subsequent investigation to determine if chemically induced colon cancer is responsive to caloric restriction in the same rodent model, colonic epithelial cell proliferation was studied as a function of moderate caloric restriction in 7-8 week old Fischer 344 rats given azoxymethane (AMO). The rats were fed an AIN diet with 5 percent corn oil *ad libitum* or at 80 percent of calories of the *ad libitum* group. Thymidine labeled colonic cell proliferation was examined in the fat mucosa of the distal colon of the rats 36 weeks after the AMO treatment. Labeled cell distribution was limited to the lower 60 percent of the crypt where the labeling index was also greater in the *ad libitum* fed animals. A 30 percent caloric restriction in a high-fat diet (23 percent corn oil) also showed a low crypt labeling index compared to rats fed the same high fat diet *ad libitum*. These results indicate that the effect of the caloric restriction in preventing cell proliferation is independent of fat intake.

Mechanisms of Dietary Restriction Effects

Although it is well documented that caloric restriction can inhibit the formation of not only rodent mammary tumors but other forms of cancer as well, the underlying mechanism for this effect remains elusive. In previous studies, food restriction of up to 50 percent reduction of the average daily ration has decreased tumorigenicity. This severe a reduction could possibly result in drastic hormonal imbalances that could have not only disrupted the normal physiology of the animals or even killed them, but may have masked other effects of dietary restriction as well. Investigators have now demonstrated that a 20 percent dietary restriction in the form of underfeeding can inhibit DMBA-induced mammary carcinogenesis by 65 percent. It was found that a 20 percent reduction in food intake resulted in no significant changes in estrogen levels as measured by radioimmunoassay. In addition, the rats in a 20 percent restricted group appeared to be cycling normally and showed no observable differences in breeding capacity. Thus, it was concluded that no significant hormonal imbalances resulted from the dietary restriction. These investigators are now exploring the possibility that changes at the cellular level in the immune system, DNA synthesis, and repair or cellular response to hormones, in addition to observed reductions in the levels of cell proliferation, act synergistically to inhibit the induction of mammary tumorigenesis by chemical carcinogens.

Growth Patterns with Modified Diet and Restricted Feeding Regimen

The maximum mean body weight of rats attained during the course of 2-year studies has increased by about 20 percent from 1975 to 1985. Higher body weights have been associated with increased incidences of various tumors. Modification of diet and feeding procedures may slow growth and lower the maximum body weight attained, which may, in turn, decrease the incidences of spontaneous tumors. A lower-protein diet may decrease the incidence and severity of kidney disease in older rats. A study has been undertaken to determine the feasibility of a 15 percent protein diet with restricted feeding from 4 p.m. to 8 a.m. in lowering the maximum body weights and decreasing the severity of nephrosis in rats in comparison with *ad libitum* feeding of a 24 percent protein diet. Body weight, feed and water consumption, and urine composition will be monitored, and tissues will be collected for histology at the end of the study.

Nutrition and Molecular Biology

Development of the techniques of molecular biology now permits penetration into the working of cells at a level previously unattainable. Molecular biology has permeated all aspects of applied, as well as basic, biomedical sciences, including metabolic and nutritional research. NIH support has been instrumental in these developments. In nutrition research, molecular biology and other basic techniques are being applied to the study of intermediary metabolism of nutrients, the measurement of tissue responses to nutrients, and the understanding of human genetic variation. Some examples of this important area of nutrition research follow.

Iron as a Virulence Factor in Pathogenic Microorganisms

The availability of iron to pathogens has been directly linked to the onset of disease in a number of illnesses associated with microbial infection. In particular, iron uptake has been shown to play an important role in the pathogenesis of septicemia and of bubonic and pneumonic plague. Activated human monocytes are now thought to inhibit intracellular multiplication of *Legionella pneumophilia*, the causative agent of Legionnaires' disease, by limiting the availability of intracellular iron.

Changes in the cell surface membrane proteins (antigens) in gonococci are a major problem in devising a vaccine against this widespread cause of sexually transmitted disease. The variability of some of the membrane antigens has now been shown to be regulated by iron molecules. Exogenous iron seems to repress the appearance of these proteins, while they appear to be readily expressed under conditions of iron starvation.

Post-transcription Gene Regulation of Iron Proteins

The two proteins that mediate the uptake and detoxification of iron in higher eukaryotes are the transferrin receptor and ferritin, respectively. Iron is delivered to most cells via endocytosis of diferric transferrin bound to the transferrin receptor. In the endosome, iron is released from the transferrin and transferred to the cytosol, where it is either utilized or sequestered in ferritin.

The expression of both the transferrin receptor and ferritin is highly regulated by the amount of available iron. Limiting iron increases the number of transferrin receptors, while plentiful iron decreases them. Ferritin level is regulated in the opposite direction, increasing in the presence of iron and decreasing in its absence. Ferritin and transferrin receptor mRNAs contain a similar cis-acting element called the iron-responsive element (IRE). These elements interact with a common iron-binding protein (IRE-BP). This protein is converted from a low-affinity form to a high-affinity form by the absence of iron, apparently by an indirect effect of iron on the oxidation-reduction state of some sulfhydryl group in the protein. (Reducing agents convert the low-affinity form to the high-affinity form, while S-S generating reagents have the opposite effect.) The iron effect has not yet been reproduced in cell lysates.

The IRE-BP in the high-affinity state binds to the 5' untranslated region (UTR) of the mRNA for ferritin, repressing its translation. It binds to the regulatory region of the 3' UTR of the TfR mRNA, repressing the degradation of the transcript. In this way, the regulated binding of the IRE-BP can coordinately regulate a decrease in the biosynthetics of the TfR by inhibition of mRNA degradation.

Metabolic Control of Osteogenesis

Researchers are testing the hypothesis that metabolic factors including oxygen supply, nutrient availability, and metabolic enzyme activity are strong determinants of osteogenesis. A homology of myoD, a gene that controls mammalian skeletal muscle differentiation, has been cloned from a rat osteoblast cell line. Plans call for determining whether this gene regulates osteoblast development from undifferentiated stem cells and how expression of this and other similar genes is regulated by cell metabolism.

Proteolipids and Mineralization of Bones and Teeth

Researchers are examining the role of proteolipids in biologic mineral formation and the mechanism of their action *in situ*. Matrix vesicle proteolipids (MVP) produced by rat chondrocytes in culture are used as a model system to test the hypothesis that MVP is a site of initial hydroxyapatite formation and that changes in the membrane environment, such as those produced by the action of vitamin-D, will alter its functional properties.

Salt Taste Reception

The taste system is the primary sensory system that regulates salt intake, which is a crucial component in the homeostatic control of sodium levels. Important progress has been made in understanding the molecular and cellular aspects of salt taste perception. Converging evidence indicates that a voltage-independent sodium channel, which is blocked by amiloride, mediates at least some components of sodium taste. Developmental studies demonstrate that taste cell receptors have an early, low sensitivity to sodium and gradually acquire increasing responsiveness. Other investigations suggest that taste receptors acquire this sodium sensitivity by adding specific membrane components that can be blocked by amiloride. For example, sodium ion channels may be added during development. Acquisition of this membrane component apparently can be blocked by dietary salt deprivation during early developmental periods in animal models.

Molecular Biology of Sweet Proteins

Intensely sweet proteins, such as monellin and thaumatin, have some interesting characteristics. They are low in calories, safe, natural, and neither introduce unnatural metabolites into the body nor perturb the balance of the amino acid pool. One of the limitations in the use of these compounds as sweeteners is their poor heat stability. Cross-adaptation and electrophysiological studies suggest that the two proteins are recognized by the same receptor. Using crystallography, nuclear magnetic resonance, and genetic engineering techniques, investigators are redesigning monellin to improve its heat stability and other physical characteristics and to facilitate site-directed mutagenesis for determining the receptor recognition site. A synthetically fused monellin has been created and is being used as a tool to identify that part of the protein which is recognized by the sweet receptor.

Computerized Testing of Sweet Compounds

Scientists interested in the molecular basis of taste and in the development of safe, noncaloric sweeteners that are also noncariogenic (do not promote tooth decay) have designed a computer model that is able to predict how a compound will taste. The molecular structures of small proteins (peptides) known to taste sweet to humans were characterized by spectroscopy and x-ray crystallography, allowing the investigators to see the size and three-dimensional structure of compounds that taste sweet. As a result of these experiments, scientists are now able to design compounds that share those same characteristics using computer simulation and to search for similar structures in already existing synthetic compounds. The computer is able to distinguish among a family of sweet-tasting compounds and also can predict whether a compound will be sweet, bitter, or tasteless. These computer models will reduce the need for panels of humans trained to taste new compounds and will make it possible to create a sweetening product that is stable when heated or stored for long periods, a stability synthetic sweeteners, such as aspartame, lack.

Gene for Defective Intestinal Glucose Transporter

Researchers have made the first identification of a genetic disease caused by a defect in a membrane transport protein. The discovery that a mutation in a membrane transport protein results in a human disease is based on research utilizing recombinant DNA technology and systems for transport protein measurement, gene cloning, and expression. The disease, glucose-galactose malabsorption syndrome, is caused by the failure of the small intestine to absorb dietary sugars. The disease is apparent within the first few weeks of life as a severe diarrhea and dehydration. The diarrhea is usually fatal unless common sugars, such as those predominant in milk, are removed from the diet. The gene coding for the intestine sugar transporter was sequenced in two sisters diagnosed with the disease. Based on biopsy samples taken from both children, a mutation was found in their DNA that changed a single amino acid in the 28th position of a chain of 664 amino acids comprising the transport protein known as the sodium glucose cotransporter. Using frog eggs as a test system, the researchers tested the function of the protein and proved that the genetic mutation eliminated sugar transport. Blood tests revealed that each parent was a carrier for the mutation in the glucose transporter gene and confirmed that the disease is an inherited autosomal recessive disease, meaning the gene must be present on the chromosomes of both the father and the mother. The disease is most prevalent in societies where familial intramarriage occurs. Researchers are currently examining the genes of other patients with the disease to determine the frequency of the mutation and to search for other mutations in the gene. They aim to develop diagnostic tests to provide earlier diagnosis and tests to identify potential carriers of the disease. The mutation also yields unique clues about the structure of the protein responsible for the transport of sugar across intestinal cell membranes.

Diet and Nutrition in Acute and Chronic Illness and Injury

Nutrition plays important and varied roles in the amelioration of a variety of acute and chronic illnesses, as well as in injury caused by trauma or surgery. The wide diversity of NIH-supported research projects in this area is illustrated by the selected examples below.

Immunology and Nutrition

Severe malnutrition due to any cause will impair the body's normal cell-mediated immunity and may diminish the immunity effected by antibodies. Lack of appropriate amounts of trace elements in the diet may contribute to severe immunologic deficits. Deficits of trace metals, such as iron and zinc, are already known to impair neutrophil function. Deficiency of the amino acid, taurine, leads to abnormalities in immune systems; decreases in the total number of disease fighting white cells; and impaired functioning of phagocytes' ability to digest and/or disintegrate invading pathogens.

The close relationship that exists between vitamin A and immune function is important for human health. Mildly vitamin A-deficient children die of infections at up to 12 times the rate of well-nourished children. Supplemental vitamin A can reduce the incidence of infectious disease. Vitamin A deficiency has a striking effect on antibody responses, primarily though impaired helper T-lymphocyte function. The problem may be due to failure to detect and transmit activation signals that occur when the immune system encounters foreign pathogens.

Food Allergy

Food allergy may play an important role in gastrointestinal disease, but little is known concerning how widespread the problem is, its mechanism of action, and its control. Upward of 34 million people may be allergic to some food ingredients. Large sums of money have been spent on unproven diagnostic and therapeutic procedures for food allergies. One long-term study has followed the natural history, immunopathophysiology, and potential diagnostic and therapeutic aspects of IgE-mediated food hypersensitivity in children with atopic dermatitis. A large percentage of children with severe atopic dermatitis for food hypersensitivity reacted to one or more foods. Abstinence from the offending food led to significant improvement in eczematous signs and symptoms and loss of symptomatic sensitivity in one-third of children studied.

The offending foods in approximately 90 percent of children with documented adverse food reactions have proven to be soy, milk, wheat, peanut, and egg. A new study is seeking to determine the specific allergens in soy and peanut protein that cause the allergic reaction and how these allergens cause this reaction. Positive reactions have caused skin, respiratory, and gastrointestinal symptoms. Initial identification and purification of the offending proteins has begun.

It is hoped that increasing recognition of the role of food allergies in disease will lead to better diagnosis, improved patient care, and eventually to the prevention of these food-induced diseases.

AIDS and Nutrition

Since the recognition of the acquired immunodeficiency syndrome (AIDS) in 1981, a coordinated and comprehensive program of basic and clinical research against AIDS and its microbial and immunological complications has been mounted. Infection by the immunologically devastating human immunodeficiency virus (HIV-1) sets the stage for weight loss and deteriorating nutritional status. Common features of advanced AIDS are anorexia, vomiting, diarrhea, malabsorption of fats, carbohydrates, protein and other nutrients, and a profound cachexia. This is particularly a problem in the areas of Africa where AIDS has reached epidemic proportions. In Africa, the clinical evolution of HIV commonly leads to a severe wasting syndrome, known descriptively as "slims disease" by the local populations. Extensive investigations into the cause of this wasting, conducted in Zaire, have concluded that AIDS-associated endogenous catabolism of fat stores is also associated with water retention, and thus actual body weight loss underrepresents the true loss of body mass. In the United States, a different study has shown that there are multifactorial reasons for the malnutrition associated with AIDS, including intestinal malabsorption, eating disorders, and systemic infections. AIDS patients were also shown to have lost more potassium than nitrogen when compared with non-AIDS patients. Other investigations of the type, severity, and causes of nutrition-related problems, such as unintentional weight loss, decreased appetite, and malnutrition, in HIV-infected individuals are continuing.

Conversely, the treatment of AIDS can be greatly facilitated by maintaining an improved nutritional status in an HIV-1 infected individual. The use of an appetite stimulant, Megace (megesterol acetate), has produced gains in weight, fat, and fat-free mass in malnourished AIDS patients. Although these patients reported an improved "quality of life," no changes in immune system parameters have yet been seen.

Vitamin A and Reduced Mortality

Clinical vitamin A deficiency affects millions of children worldwide, and subclinical deficiency is even more common. Supplemental vitamin A has been reported to reduce mortality among these children, but such findings have been questioned. Investigators conducted a randomized, controlled, masked clinical trial for 1 year in southern India involving 15,419 preschool-age children who received either 8.7 µmol (8333 IU) of vitamin A and 46 µmol (20 mg) of vitamin E (treated group) or vitamin E alone (control group). Vitamin supplements were delivered weekly by community health volunteers who also recorded morbidity and mortality. The risk of death in the group treated with vitamin A was less than half that in the control group. The risk was most reduced among children under 3 years of age and among those who were chronically undernourished, as manifested by stunting. The symptom-specific risk of mortality was significantly associated with diarrhea, convulsions, and other infection-related symptoms. Thus, the regular provision of a supplement of vitamin A to children, at a level potentially obtainable from foods, in an area where vitamin A deficiency and undernutrition are documented public health problems, contributed substantially to children's survival; mortality was reduced on average by 54 percent.

Eye Disease and Nutrition

The Eye Disease Case-Control Study is a five-center study designed to investigate risk factors for neovascular/exudative age-related macular degeneration, central retinal vein occlusion, branch retinal vein occlusion, idiopathic macular hole, and rhegmatogenous retinal detachment. Between 1986 and 1990, data were collected from interviews, ophthalmic examinations, other clinical examinations, and laboratory analyses of blood specimens. A logistic regression function with adjustment for age, sex, clinic, and patient source (private vs. nonprivate) indicated a statistically significant protective effect against neovascular/exudative macular degeneration for higher carotenoid levels. An antioxidant index derived from nutrients with antioxidant potential also showed a statistically significant reduced risk of age-related macular disease with higher levels of the index.

Nutrition and Trauma

Changes in metabolic patterns and nutritional status play an important role in the development of sepsis and multiple organ failure, as well as in the recovery from severe injury, including surgical trauma. Recent highlights in the area of nutritional requirements and therapy in the traumatized patient have focused on the effects of diet in the development of septicemia following surgical and burn injury.

Specifically, bacterial infection is a frequent and serious problem in patients who survive the initial shock phase of thermal injury. Infections in burn patients generally have been considered to arise from exogenous organisms colonizing the burn wound. Until recently, very little attention has been directed to the indigenous microflora in the gastrointestinal tract of the burn patient as a source of the repeated episodes of bacteremia; yet, the gut may serve as a reservoir for organisms causing bacteremia in the burn patient. Bacterial translocation has been defined as the passage of viable bacteria from the intact gastrointestinal tract to the mesenteric lymph nodes and eventually into the systemic circulation. It has been speculated that the gastrointestinal tract may cause the infections, either indirectly by fecal organisms contaminating and colonizing the wound, or directly by passage through the intestinal wall. Researchers have shown that feeding animals an elemental diet promotes spontaneous bacterial translocation and increases mortality in these animals after an injection of *E. coli* endotoxin. Endotoxin challenge also was associated with higher levels of serum tumor necrosis factor (TNF), an endotoxin-induced macrophage product which produces cachexia. Although the mechanisms responsible for these changes are not known, these investigators have speculated that mortality related to bacterial translocation may in part be an amplified cytokine response to endotoxin.

Grantees also have demonstrated that chronic administration of TNF in experimental animal models reproduces many of the physiologic findings observed in the chronic wasting of clinical disease. During repeated doses of TNF, there is a consistent decrease in food intake in rats and mice, decreased nitrogen balance, and weight loss. Concomitant administration of antibody to TNF is successful in blocking these effects. Chronic starvation elicits a preferential mobilization of fat stores, with a relative sparing of skeletal muscle. Also, in acute starvation, there is a marked wasting of liver protein accompanying the loss in peripheral mass. By contrast, chronic TNF administration produces an exaggerated peripheral skeletal muscle wasting, with a preservation of liver mass similar to that observed in injured patients. Researchers also have demonstrated that TNF markedly suppresses the activity of lipoprotein lipase, the enzyme that catalyzes the hydrolysis of lipoprotein derived triacylglycerol, providing fatty acids for storage or catabolism.

Total parental nutrition (TPN) has favorably influenced the clinical outcome of many malnourished and injured patients unable to receive nutrients by the enteral route. Recent evidence suggests that significant differences in response to infectious insult may exist between the enterally and parenterally fed states. These investigators have produced data that suggest that bowel rest produces alterations in host resistance to injury, independent of malnutrition. Other investigations are providing evidence that intravenous refeeding blocks growth hormone provoked rises in serum free fatty acids. In addition, hyperalimentation induces a metabolic background that inhibits growth hormone secretion.

Surgery and Nutrition

Morbidity and mortality following surgery and trauma have improved considerably over the years because of diligent attention to meeting fluid and electrolyte needs, blood replenishment, antibiotic treatment, nutritional management, and other ancillary support services. Surgery and trauma induce a hypermetabolic state and are usually accompanied by a decreased intake of nutrients. Concomitantly, there is a decrease in immune function, as exemplified by microbes traversing the intact gut epithelial barrier. The entry of viable bacteria and fungi into the intestinal tissues is a common and early consequence of surgery and is enhanced by factors such as shock, antibiotic compromise of the anaerobic bacterial flora, and bowel obstruction. The elaboration of endotoxins by these microorganisms further accelerates this process and may lead to liver involvement, and in serious cases, to sepsis and multiorgan failure. Early feeding after injury decreases the incidence of infection and dampens the hypermetabolic response.

Two animal models have been established to study these processes. A guinea pig model has been used to dissect the immunological events occurring as bacteria and endotoxin traverse the intact epithelium of the intestine and initiate the infectious process and hypermetabolic state. Individual components of the inflammatory response are being evaluated. The sequential interplay of these various components is being studied in order to identify critical steps in the process amenable to intervention. The role of nutritional factors, such as omega-3 unsaturated fatty acids, in ameliorating this process is being evaluated. A new guinea pig model for peritonitis has been used to evaluate the effect of nutritional factors on survival. The optimal diet contained reduced protein and had 56 percent of calories contributed by lipids with equal amounts of omega-3 and omega-6 fatty acids represented by fish and safflower oils.

Altered Gastric Emptying in Patients with Head Injuries

It is thought that adequate nutrient administration may improve the outcome of head injured patients and hasten recovery. Achieving this is difficult, however, because these patients are usually hypermetabolic and hypercatabolic, requiring increased amounts of nutrients. Most patients suffering from various types of trauma do not tolerate enteral feedings postinjury; this intolerance is more prolonged in those with moderate to severe head injury. The association between severity of head injury, increased intracranial pressure, and tolerance of enteral feedings suggests a link between the injured brain and the non-functioning gut. A recent study of head injured patients showed that they often experience alterations of gastric emptying which may affect their ability to tolerate enteral feedings. Further research is needed to determine the cause of this difficulty and identify agents which can modify the gastric response.

Enteral and Parenteral Nutrition Support

A variety of other studies in the area of nutrition support of patients are being undertaken by NIH researchers. These include:

- Determination of the role of nutrition as a pressure sore risk factor.

- Examination of the effect of minimal preoperative changes in diet and lifestyle on the alteration of circadian timing associated with surgery and subsequent fatigue and activity alterations.

- Determination of whether immunoregulatory peptides are involved in loss of food appetite with tumor growth and what cells secrete them; whether suppression of food intake with tumor growth or infection is associated with changes in gastric motility or plasma levels of glucoregulatory hormones; and whether nutritional supplements affect nutritional status, immune cell function, or tumor growth in the infected or tumor-bearing host.

- Identification of external measurements for predicting the insertion lengths of nasogastric tubes in children in order to provide specific guidelines to improve insertion techniques of hospital and home care providers.

HIGHLIGHTS OF NUTRITION RESEARCH: CENTERS AND PROGRAMS

Nutrition Research in the Clinical Nutrition Research Units

As a means of encouraging a multidisciplinary approach to clinical nutrition research, the NIH has sought to foster the development and operation of Clinical Nutrition Research Units (CNRUs) through the establishment of a CNRU program in 1979. Two NIH institutes, the NIDDK and NCI, support these units. The CNRUs supported by the NCI focus on cancer prevention. Specific objectives of a CNRU are as follows:

- To create or strengthen a focus in a biomedical research institution for multidisciplinary research in clinical nutrition, in order to develop new knowledge about specific nutrients in health throughout the human life cycle, and in the prevention and treatment of disease.
- To strengthen training environments in order to improve the education of medical students, house staff, practicing physicians, and allied health personnel in clinical nutrition.
- To enhance patient care and promote good health by focusing attention on clinical nutrition and generating nutritional information for the public.

The essential components of a CNRU include the following elements:

- Research with human subjects and populations;
- Laboratory investigations;
- Research training (funds derived from other sources);
- Shared facilities and research resources;
- Education programs for medical students, house staff, practicing physicians, and allied health professionals (funds derived from other sources);
- Research components of nutritional support services;
- Public information activities (funds derived from other sources).

To qualify for the award of a CNRU grant, the potential applicant institution or consortium of institutions must already have a substantial base of ongoing, independently supported, peer-reviewed research in the nutritional sciences. This initial required research base is formed from a group of investigators with individually funded research projects who can benefit from shared resources. Thus, the CNRU grant is intended to provide an added dimension that includes the capability and the potential for accomplishments greater than that possible by the support of individual projects alone.

A CNRU must be an identifiable organizational unit within a single university medical center or a consortium of cooperating institutions. The overall goal of a CNRU is to bring together, on a cooperative basis, basic science and clinical investigators in a manner that will enrich the effectiveness of research in nutritional sciences. A program of excellence in biomedical research in this area must be in existence at the time of submission of a CNRU application. Close cooperation, communication, and collaboration among all center personnel of many professional disciplines are characteristics of a successful CNRU. A successful CNRU also will attract into the CNRU talented scientists from disciplines other than nutrition.

The major source for support of biomedical research projects associated with the CNRU is derived from the separately funded projects of the participating investigators. Similarly, stipends for professional trainees in research are not available through CNRU funding; rather, such funding must be sought through other mechanisms.

Core facilities of CNRUs are developed to support research in the broad areas of fundamental and clinical nutrition. Application of state-of-the-art techniques in the areas of cell biology, molecular biology, immunology, and integrative physiology is encouraged to increase knowledge concerning the function and requirements of nutrients, the relationship of diet (and nutrients) to health and disease, and the prevention and treatment of disease as an outgrowth of nutrition research.

Core facilities in a CNRU are shared resources that enhance productivity or in other ways benefit a group of investigators working to accomplish the stated goals of the CNRU. Two other types of activities also may be supported with CNRU funding--a pilot and feasibility program and an enrichment program. The pilot and feasibility program provides modest support for new initiatives or feasibility studies for new investigators who are in research areas of direct interest to the CNRU. These areas may include biomedical, epidemiologic, or behavioral research as they pertain to the CNRU goals. The enrichment program provides limited funds to sponsor seminars, visiting scientists, workshops, etc.

Brief descriptions of the activities of CNRU facilities in FY 1990 are given below:

- The CNRU at the University of California, Davis (supported by NIDDK) promotes interdisciplinary research among nutrition scientists in the Schools of Medicine and Veterinary Medicine and in the College of Agriculture. Four general research themes are encompassed: nutritional consequences of disease and trauma, intestinal absorption of nutrients, regulation of food intake and body weight, and nutrient regulation of gene expression. Research in these areas is supported by centralized core laboratories which provide assays of vitamins and minerals, metabolic substrates, and clinical biological samples, and which support methodologies in molecular and cell biology and in studies of food intake. Funds from the CNRU are applied directly to support a new investigator and six pilot and feasibility studies in clinical nutrition. An enrichment program has heightened the visibility of clinical nutrition research in the university, through support of regular scientific seminars and a visiting professor program.

Researchers at the CNRU have recently demonstrated:
- fat malabsorption and jejunal morphological abnormalities occur in HIV-infected patients and that evidence of HIV infection of inflammatory cells and enterocytes within the intestinal mucosa can be detected;
- the lack of liver injury in the presence of compromised antioxidant defense in alcohol-fed animals may be explained by an increased membrane saturated/polyunsaturated fatty acid ratio;
- very obese women have subnormal levels of serum phospholipid arachidonate, which rise to normal levels during diet-induced rapid weight loss, then return to previously depressed values during refeeding and maintenance of weight loss; and
- energy expenditure is blunted in the genetically obese Zucker rat as early as the first 2 days of life.

- The principal aim of the CNRU at the University of Alabama in Birmingham (supported by NCI) is to generate, promote, and strengthen interdisciplinary research in clinical and basic nutrition, emphasizing the prevention of disease, primarily cancer, and the improvement of patient care. The provision of shared resources in the form of nutrition research support, clinical, nutrient data bank, experimental carcinogenesis, histopathology, statistics, and image analysis core laboratories/facilities and the support of starter grants for young investigators are the main mechanisms used for promotion of nutrition research. The educational objectives of the CNRU, including research on the development and evaluation of educational methodologies, are served by a nutrition education component and a nutrition information service.

Recent scientific accomplishments include:
- demonstration of improvement in pre-neoplastic lesions of the cervix and the bronchial epithelium by folate and vitamin B_{12} supplementation;
- synthesis and evaluation of new potential chemopreventive retinoids;
- discovery of a new bone cell adhesion phosphorylated protein, osteopontin, that may be involved in cancer promotion; and
- demonstration of initiation-facilitation of experimental mammary carcinogenesis by ethanol.

- The CNRU at Memorial Sloan-Kettering Cancer Center (supported by NCI) is becoming the central mechanism for the major nutrition efforts of the participating institutions, i.e., Memorial Sloan-Kettering Cancer Center, Cornell University Medical College, Rockefeller University Hospital for Special Surgery, and North Shore University Hospital. Core laboratories focus on metabolism and oncology, carcinogenesis and nutrition, biophysics, immunology, and metabolic bone disease. The CNRU Nutrition Information Center was established in the second year of this program. Its activities continue to involve development of a nutrition "Hotline" and initiation, collection, and dissemination of nutrition materials to the professional community first and later to the general public.

Recently, CNRU researchers have:
- shown that gallium nitrite is an effective and safe therapeutic agent for treatment of the hypercalcemia of malignancy;
- found that patients with nutritional dwarfism have low levels of Na^+, K^+-ATPase activity;
- developed novel approaches to malaria chemotherapy through selective

interference with riboflavin metabolism; and
- shown that a low-fat diet with an optimal ratio of omega-3 to omega-6 fatty acids can inhibit mammary tumor metastasis in an animal model and that dietary linoleic acid also is required for this effect.

- The University of Washington CNRU (supported by NIDDK) encompasses a wide ranging scope of nutrition-related research being conducted in a diversity of disciplines. Studies range from in-depth basic research, nutritional studies using laboratory animals, metabolic ward, and outpatient clinical investigation, to epidemiological and intervention studies. The overall goal of these studies is to provide an in-depth, better understanding of the physiology of fuel utilization and clinical disorders that can be related to nutrition, both from a causal and therapeutic standpoint. Several major areas are under investigation, including nutritional aspects of atherosclerotic heart disease, diabetes, lipid metabolism, metabolic bone disease, obesity, nutrition in the elderly, and nutrition and cancer. The two research cores of the CNRU are: a laboratory core to provide affiliate investigators with cost-efficient, state-of-the-art nutritional assays and to help with new method development; and a clinical nutrition core to provide facilities and help for investigators with their clinical research and to provide a patient registry and biostatistical unit.

Research conducted recently by investigators at the CNRU has indicated that:
- net regression of atherosclerotic lesions can be demonstrated in a short period by appropriate and marked lipid-lowering therapy with diet and drugs;
- exercise training in the elderly is associated with beneficial changes in the ratio of abdominal to subcutaneous fat without a change in lean body mass;
- calcitonin and biphosphonates are important in the prevention of bone loss in elderly women and that 1,25-dihydroxyvitamin D_3 is ineffective in the treatment of postmenopausal osteoporosis; and
- education and good adherence to a low-fat, low-cholesterol diet can lead to a 10-15 percent reduction in plasma and LDL cholesterol levels that is maintained over a 2-year period.

- The CNRU at the Oregon Health Sciences University (supported by NIDDK) is exploring the relationship of diet to disorders of the cardiovascular system and degenerative disorders of the elderly that track with cardiovascular disease. Specifically, the CNRU focuses on the impact of dietary intakes of calcium and lipids and their metabolism on the occurrence and/or treatment of hypertension (including alcohol-induced hypertension), hyperlipidemia, toxic nephropathy, cataract formation, and type II diabetes. Core facilities in biostatistics and nutrient assessment, hormone and mineral metabolism, lipid metabolism, cell calcium, and vascular physiology serve to facilitate the collaborative projects, research training, and investigative programs of the Nutrition Support Service.

Recent findings from the CNRU have indicated that:
- glycation of HDL *in vitro* inhibits the capacity of HDL to promote cholesterol efflux from cultured cells and that this mechanism may contribute to the development of athersclerosis in diabetes;
- short-chain n-3 fatty acids in commercial infant formula are inferior to the longer-chain n-3 fatty acids present in human milk in supporting brain development in a chick model;
- a synergy exists between dietary calcium and calcium channel blockade in stabilizing abnormal vascular smooth muscle Ca^{2+} currents in stroke-prone hypertensive animals; and
- the duodenal calcium-binding protein mechanism is abnormal in experimental hypertension and can be corrected, in part, by increasing dietary calcium intake.

- The CNRU at the University of California - Los Angeles (supported by NCI) seeks to promote both clinical and fundamental research on the role of nutrition in cancer prevention and cancer treatment; encourage advancements in nutrition education at the UCLA hospitals and campus; and foster an interdisciplinary approach to problems in cancer nutrition. The CNRU is organized around four core laboratories: the vitamin/trace element core, the lipid-hormone core, the stable isotope core, and the cellular molecular biology core.

  Results of recent studies at the CNRU have indicated that:
  - total blood cholesterol could be used as an indicator of dietary adherence in association with changes in body weight that occur when fat intake is decreased;
  - megesterol acetate promoted increased consumption of calories and preferential selection of high-fat foods and led to significant weight gains in patients with advanced breast cancer and lung cancer;
  - a methyl-donor-deficient diet in rats leads to increased numbers of breaks in the genetic material, DNA; and
  - breast fat tissue and abdominal fat tissue correlated with the incidence of breast cancer in female rats given a carcinogen, suggesting a specific role for fat tissue in breast cancer promotion.

- The CNRU at the University of Chicago (supported by NIDDK) assists the many physicians and scientists at the University in their research programs related to basic nutritional biology and clinical nutrition. This is accomplished through the efforts of six core laboratories that provide special scientific expertise in: energy, fat, carbohydrate, and protein metabolism; vitamin and bone mineral assays; research in lipids and lipoproteins; trace element assays and metabolism; hormonal regulation of nutrient metabolism; and nutrition assessment and support. A major focus of the CNRU is the use of stable isotopes for nutritional and metabolic studies.

  Research performed at the CNRU has demonstrated that:
  - calcium and/or vitamin D can affect mutations in cancer-promoting genes, influence the structure and function of colonic cell membranes, and alter aspects of cell biochemistry related to malignant transformation;
  - traditional ways of estimating caloric requirements for patients with Down's syndrome represent overestimates and may be contributing to the obesity that is so prevalent in this patient group;
  - obese subjects often have increased circulating lipoprotein levels after meals, which may play a role in the increased risk of athersclerosis with obesity; and
  - vitamins D, E, C, and folate all appear to influence the development of cancer in ulcerative colitis.

- At Vanderbilt University, the CNRU (supported by NIDDK) comprises an administrative core, analytical laboratory core, nutrient transport core, mass spectrometry core, and energy balance core. The core facilities have been instrumental in:
  - developing methods for tracing intracellular movement of ions;
  - developing a unique method for converting spontaneous movement into energy force using a suspended floor inside a live-in calorimeter;
  - developing and validating direct assays for thiamin and thiamin pyrophosphate, apolipoproteins, and muscle membrane fluxes; and
  - developing newer analyses for lipid mediators, such as epoxyeicosatrienoic acids, using negative ion mass spectrometry in combination with stable isotope dilution methodology.

  Ongoing studies at the CNRU include:

- the role of fatty acids in glomerular receptors and functions;
- examination of the three-dimensional structure of retinol-binding protein with its carrier protein transthyretin;
- vitamin A deficiency in mice infected with respiratory syncytial virus ;
- the role of vitamin D and estrogen in the metabolism and differentiation of osteoblasts; and
- ethanol-thiamin interactions in energy metabolism.

Nutrition Research in the General Clinical Research Centers Program

The General Clinical Research Centers (GCRCs) Program, initiated in 1960 and administered by DRR, now part of the NCRR, supports a nationwide network of 74 centers for clinical research within hospitals of academic medical institutions. At these centers, multicategorical clinical research is conducted on many common and rare diseases. The GCRCs are usually discrete units within major hospitals. They provide an infrastructure for clinical research by investigators who receive their primary funding for research from components of the NIH other than the NCRR. As a result, the research carried out in the GCRCs reflect the missions of several NIH institutes, including cancer, heart disease, infectious diseases, diabetes, neurological diseases, obesity, arthritis, and aging. GCRCs also provide a hospital's resident physicians and medical students the opportunity to learn and participate in the translation of basic and clinical research findings into established medical practice. Clinical evaluations at the GCRCs focus predominantly on phase I and early phase II trials of new drug treatments and other aspects of therapy. Prevention research includes studies of immunizations, control of blood pressure, dietary lipids, smoking habits, infectious and toxic agents, and alcohol and drug abuse.

Several nutrition-related research highlights from the GCRCs program follow.

Taurine Nutrition in Patients Undergoing Long-term Total Parenteral Nutrition

Investigators at the Harbor-UCLA Medical Center are studying taurine metabolism by stable isotope methodology in healthy volunteers and in patients with chronic renal failure or chronic liver failure. The hypothesis to be tested is that under certain conditions, humans may have a nutritional requirement for taurine.

Taurine is a unique amino acid which, until recently, had been neglected in studies of human amino acid metabolism. Taurine is a B-amino acid and a sulfonic acid, rather than a carboxylic acid. It is not found in mammalian protein, yet taurine is the most or second most abundant free amino acid in animals, including humans. In humans, there are few pathways for the metabolism of taurine. Several studies suggest that an exogenous intake of taurine may be necessary to maintain normal plasma taurine levels and a normal percent of bile conjugates of taurine in premature infants and full-term infants. However, virtually no study has directly addressed whether children and adults need exogenous taurine. The kinetic studies of taurine metabolism at the Harbor-UCLA Medical Center are part of an overall study of the requirement for taurine in humans. During the first three years of this study, the investigators examined whether there is a nutritional requirement for taurine in children and adults on long-term total parenteral nutrition (TPN). Their current results indicate that long-term TPN patients not given taurine have significantly reduced taurine levels in plasma, platelets, and urine and, in adults, in red cells and granulocytes and the percentage of bile acids conjugated to taurine. Eyeground appearance and dark adaptation were frequently abnormal, and the electroretinogram (ERG) was abnormal in all children and in approximately 45 percent of adults tested. Treatment with taurine, 10 mg/kg/day intravenously, normalized many cellular taurine levels and may have improved liver function in adults; visual function did not improve significantly, possibly because some damage is permanent. However, the ERG implicit times that were normal at the onset of study became abnormal more often in the adult TPN patients not receiving taurine.

Preliminary kinetic study data with ^{13}C-taurine suggest that adult TPN patients have decreased synthesis and body pools of taurine compared to normal adults. These investigators' kinetic and compartmental studies of taurine metabolism currently represent the largest and most extensive tracer studies of taurine in humans. Studies will be extended to include studies of taurine metabolism in patients with chronic renal failure or chronic liver failure.

The Behavioral and Cognitive Effects on Children of Diets High in Sugar and/or Aspartame

There is much anecdotal information suggesting that sugar stimulates hyperactive behavior and/or attention deficit disorder in children, but good experimental data are lacking. Researchers at the University of Iowa are conducting a double-blind crossover study designed to examine the effects of diets high in sucrose and/or aspartame on behavioral and cognitive performance in children. Normal school-age children, children with attention deficit hyperactivity, children reported to respond adversely to sugar, and normal preschool children are being studied. Three diet conditions of 1 month each are utilized in a Latin square design. Weekly behavior and cognitive performance measurements include attention span, activity level, and impulsivity. In addition, assessments are made of learning ability and academic performance from measurements obtained at home, school, and in the laboratory. Serum samples are assessed for glucose, amino acids, and erythrocyte aspartylphenylalanine dipeptidase levels. Markers of ascorbic acid and riboflavin are used to assess compliance. Subjects, their families, and the research staff are blinded to insure compliance with the diets. In 1991 the study codes will be broken and data analysis will begin. Completion of a carefully controlled study will offer much needed data to physicians and families about the roles sugar and/or aspartame may play in the stimulation of hyperactivity and will assist food manufacturers who are pressured to add detailed information about sugar on food labels.

Growth of Breastfed Infants

Reliable information on the energy requirements of normal young infants is an essential prerequisite to a clear understanding of the nutrient needs of normal infants who cannot be or are not breastfed. This information also provides an essential base to which the extra needs of malnourished infants can be added. The cumulative results of recent direct measurements of energy expenditure, utilizing the double-labeled water technique, have indicated that energy requirements are substantially lower than recommendations that have been widely accepted in this country and elsewhere. These revised estimates are in accord with recent calculations of the energy intake of normal fully breastfed infants, though reliable data on the latter are still quite sparse.

The results of the current study at the University of Colorado have substantially augmented these data. A 7-month longitudinal study of 60 healthy breastfed infants has been undertaken. The cumulative growth of these infants at 3 months was virtually identical to the currently accepted median for normal infants despite an energy intake at 3 months of only approximately 80 kcal/kg/day, or 80 percent of current recommendations. Energy expenditure of breastfed infants has been found not to differ significantly from that of formula-fed infants. These findings provide further support for the concept that energy requirements of young infants are substantially lower than previously thought. Mean growth percentiles for weight and length declined slightly in this study group between 3-7 months of age. Additional research will be necessary to determine if this can be accepted as a normal growth pattern for older breastfed infants or whether supplemental foods were desirable for a substantial percentage of breastfed infants at 3-4 months. A maternal zinc supplement administered in a randomized double-blinded study design did not affect milk zinc concentrations or infants' growth, indicating that current maternal zinc intakes (greater than 10 mg/day) are generally adequate to maintain normal breast milk zinc concentrations.

Effect of Dietary Protein on Renal Function, the Renin-Angiotensin System, and Nutritional Status in Patients with Chronic Renal Transplant Rejection

Dietary protein restriction reduces proteinuria and slows the progression of renal failure in a variety of renal diseases in native kidneys. Such beneficial effects may be mediated by the multiple renal effects of dietary protein, including those on glomerular capillary hemodynamics, the renin-angiotensin system, renal growth, ammoniagenesis, and metabolic rate. A study was undertaken at the University of Minnesota to examine the effects of dietary protein restriction in patients with chronic renal transplant rejection.

Fourteen patients with biopsy-proven chronic renal transplant rejection who had been on a self-selected diet of 1.0 ± 0.1 g protein/kg/day were randomly assigned using a crossover design to two 11-day periods, one period on a low protein diet (0.55 g/kg/day) and the other on a high protein diet (2 g/kg/day). The effect of these diets on renal hemodynamics, plasma renin activity, proteinuria, and nutritional status was examined.

The low protein diet was associated with a significant improvement in glomerular permselectivity in all patients as evidenced by a significant fall in the fractional clearance of albumin and IgG and reduction in 24-hour urinary excretion of total protein, albumin, and IgG without any change in blood pressure, glomerular filtration rate, or renal plasma flow. Compared to the proteinuria at the beginning of each diet, a high protein diet did not increase proteinuria, but a low protein diet significantly decreased the proteinuria. The low protein diet was also associated with a significant reduction in plasma renin activity, suggesting that part of the beneficial effect of protein restriction was related to the suppression of the renin-angiotensin system. Protein restriction was also associated with a modest but significant fall in serum proteins.

A low protein diet reduces proteinuria and lowers plasma renin activity in patients with chronic renal transplant rejection. Dietary protein restriction may ameliorate chronic rejection partly by suppressing the renin-angiotensin system. In chronic rejection, restriction of dietary protein should be modest and the nutritional status of the patient followed closely.

Interaction Between Salt and Calcium on both Blood Pressure and Renal Blood Flow

Approximately 50 percent of essential hypertensive patients can be classified as "salt-sensitive" as determined by their blood pressure (BP) responses to high and low salt intakes. It is becoming clearer that salt does not act alone in causing its hypertensive effects. Past studies have demonstrated that calcium and sodium intake interact to determine salt sensitivity in black and oriental subjects. Specifically, a low calcium intake increases salt sensitivity in these populations.

A study undertaken at the Brigham and Women's Hospital was designed to determine the interaction between salt and calcium on both blood pressure and renal blood flow (RBF). Blood pressure and renal blood flow (PAH clearance) were measured in 21 hypertensive patients (19 Caucasian, 2 black) after 7 days on a low salt/low calcium diet and again after either a high salt/high calcium diet (HS/HC) or a high salt/low calcium (HS/LC) diet for another 7 days. For the first diet period, all subjects consumed a high salt intake

(225-250 mEq Na/day). This diet contained either 350-400 mg calcium (designated high salt/low calcium, HS/LC, n=12) or 1,000 mg calcium (designated high salt/high calcium, HS/HC, n=9). For the second week, all subjects consumed a low salt (10 mEq Na/day), low calcium (350-400 mg/day) diet. All the food was provided by the facility's metabolic kitchen on an outpatient basis. The patients were seen in the outpatient Clinical Research Center every other day to measure their blood pressure, to deliver their daily 24-hour urine collections, and to obtain their food. The blood pressure effects of the diets were defined according to the blood pressures on the final day of each diet (12 measurements during one hour in the supine position).

Compared to low salt BP, both high salt diets increased BP, but the increase with high salt/low calcium was significantly greater than with high salt/high calcium (+14.6 ± 3.9/+8.2 ± 1.7 mm Hg versus +7.5 ± 1.9/+2.5 ± 1.4; systolic/diastolic; both p<or= 0.05). PAH clearance increased 26 ± 13 cc/min/1.73 m^2 on the HS/HC diet but only 10 ± 17 cc/min/1.73 m^2 on HS/LC (p = 0.05 between groups).

These data suggest that a low calcium diet may contribute to the phenomenon of salt sensitivity. The low calcium intake appears to affect both the systemic and renal vasculature.

Nutrition Research in Other Centers

The center mechanism has proven useful in providing support for long-term multidisciplinary programs of research and development in critical health problem areas. Nutrition research is an important component of the programs of many of the centers supported by the NIH. Highlights of nutrition research conducted at a variety of specialized centers include the following:

- New York Obesity Research Center at St. Luke's-Roosevelt Hospital Center, Columbia University, Rockefeller University, and Cornell University (supported by NIDDK).

The aim of the Obesity Research Center is to foster interdisciplinary cooperation of a group of investigators conducting programs of high-quality research related to obesity. The research programs of the Obesity Research Center focus on the following thematic areas: molecular biology, adipocyte metabolism, energy expenditure, body composition, the pathological consequences of distribution of body fat, the regulation of caloric intake, the clinical treatment of obesity and of its effects, and animal models of obesity. Examples of the topics of ongoing studies include identification of the genes(s) responsible for obesity in the ob and db mouse; the expression of neuropeptide Y, a candidate satiety-inducing substance in the central nervous system, in rodent hypothalamus; the relation of body composition to energy expenditure; the effects of the peptides cholecystokinin and bombesin on food intake; the effect of iopanoic acid in protecting the loss of lean body weight during dieting; and possible ethnic differences in lipoprotein lipase activity in human adipocytes from different sites in women with upper and lower body fat.

- Nutrition and Chronic Disease CNRU at the University of California, Berkeley (supported by NICHD).

This program is a multidisciplinary, interinstitutional project concerned with the relationship of nutrition and chronic disease. Core laboratories are dedicated to nutrition and metabolism, radioimmunoassay, tissue culture, and biochemical analysis. Areas of interest include nutritional requirements, nutritional deficiencies, and assessment of nutritional status in renal, liver, neurological, and gastrointestinal disorders; diabetes mellitus; obesity; and hematological disease. Ongoing research projects include an examination of zinc homeostasis in pregnant diabetic women, a study of Megace therapy and weight gain in patients with AIDS, a survey of risk factors for noninsulin-dependent diabetes among Australian aborigines, and an analysis of factors related to the development of infant macrosomia.

- Chemosensory Clinical Research Center at the Monell Chemical Senses Center, University of Pennsylvania Smell and Taste Center, and Connecticut Chemosensory Clinical Research Center, University of Connecticut Health Center (supported by NIDCD).

  The activities of the clinical chemosensory research centers include nutritional management to rehabilitate or maintain the quality of life in patients with taste or smell disorders. The nutritional assessment of the patients with appropriate dietary intake measurements, dietary and weight history, food behavior questions, and anthropometric measures enables nutritionists to identify potential nutritional problems and to provide guidance for dietary behavior modification.

- Core centers for research in mental retardation at the University of California, Los Angeles; the University of Colorado Health Sciences Center; and the Kennedy Institute for Handicapped Children in Baltimore (supported by NICHD).

  The centers provide central support for a multifunded, interdisciplinary research and training program in mental retardation. Nutrition-related research conducted at these centers has included investigations of the effects on brain development of chronic undernutrition over several generations; the development of a hypoketonemic animal model through dietary manipulation; studies of the role of trace metals, especially copper, zinc, and chromium, as well as undernutrition and environmental deprivation, in brain development; studies on the efficacy of an arginine restricted diet in further progression of chorioretinal degeneration in patients with gyrate atrophy; and investigations of treatment with low tryptophan diets and specific serotonin antagonists on feeding, sleeping, and other behaviors in patients with urea cycle enzymopathies.

- Centers for research in the environmental health sciences at the University of Medicine and Dentistry of New Jersey--R.W. Johnson Medical School; the University of California, Berkeley; the University of Rochester; and the University of Cincinnati (supported by NIEHS).

  The programs of these centers are intended to enhance the understanding of environmental hazards affecting human health. Nutrition-related research conducted in the various centers includes toxic and essential metals, nutritional impact on toxicity and carcinogenesis, and dietary exposure to toxic substances.

Examples of other centers which include a nutrition research component include the following:

- Specialized Centers for Research in Arteriosclerosis at Wake Forest University; the University of California, San Diego; the University of California, San Francisco; the University of Iowa; and the University of Chicago (supported by NHLBI)

- Specialized Centers for Research on Osteoporosis at Creighton University and the Helen Hayes Hospital (supported by NIAMS)

- The Research Center in Oral Biology at the University of Pennsylvania, Philadelphia; the Rochester Caries Research Center at the University of Rochester; and the Specialized Caries Research Center at the Forsyth Dental Center, Boston (supported by NIDR)

- Centers for the study of liver disease at the University of California, San Francisco; the University of Minnesota of Minneapolis-St. Paul; and Yeshiva University (supported by NIDDK)

- Diabetes-Endocrinology Research Centers and Diabetes Research and Training Centers (supported by NIDDK)
- Perinatal Research Emphasis Centers (supported by NICHD)
- The Center for Research on Developmental Disabilities at the University of Minnesota of Minneapolis-St. Paul (supported by NICHD)
- Centers for research in reproductive biology/physiology at the University of Pittsburgh and Vanderbilt University (supported by NICHD)
- Centers for burn/trauma research at the Cornell University Medical Center, New York, and Brigham and Women's Hospital, Boston (supported by NIGMS)

Nutrition Research in the Programs

Support from the Biomedical Research Technology Program (NCRR) has led to findings on growth hormone and whole body protein homeostasis and the effects of exercise and growth hormone on protein turnover.

Researchers are using the Washington University's Resource for Biomedical Mass Spectrometry to study a population of children who exhibit a failure to grow. This state-of-the-art resource provides the means of studying the metabolic fate of amino acids, the building blocks of protein, by labeling them with nitrogen-15 and then measuring its excretion in urine using isotope ratio mass spectrometry. Because the overwhelming proportion of chemically identical natural nitrogen has an atomic weight of 14, the measurement of nitrogen-15 gives a direct indication of the metabolic fate of the labeled amino acids. The investigators are studying the acute effect of growth hormone on protein homeostasis, the processes that regulate the buildup and breakdown of protein, and then they plan to correlate this acute effect with long-term growth. The results should be useful in understanding the process of growth hormone effects on protein metabolism and growth and conceivably could lead to improvements in therapy for children who fail to grow properly.

Researchers using the Washington University Resource for Biomedical Mass Spectrometry are studying the rate of protein metabolism in adults who undergo 12 weeks of heavy resistance exercise training concurrently with daily administration of growth hormone. The mass spectrometer allows the researchers to estimate protein metabolism from measurements on excreted nitrogen products in urine and exhaled carbon dioxide, following the infusion of two amino acids, leucine and glycine, that have been synthesized from nitrogen-15 and carbon-13, chemically identical isotopes with heavier atomic weights than the commonly occurring nitrogen-14 and carbon-12, which constitute the overwhelming majority of nitrogen and carbon atoms in nature. By following changes in the excreted isotope ratio, the researchers are able to estimate protein metabolism. The results should enhance knowledge of the effects of growth hormone on protein metabolism during the course of intensive exercise and perhaps lead to improvements in therapy on growth hormone administration.

Two studies supported by the NCRR's Biomedical Research Support Program at University of Health Sciences/the Chicago Medical School concern appetitive and cognitive function in noninsulin dependent diabetes mellitus (NIDDM). The study on the appetitive function was undertaken because many NIDDM patients report that food craving prevents them from adhering to their prescribed diets. Patients were asked to complete a questionnaire that compared desired versus actual intake of six food groups: sweet foods, salty foods, starches, fruits, meats, and dairy products. Factor analyses separated two food preferences: basic diet foods and high-taste foods. The degree of craving, i.e., the desire to consume more than actual intake, was significantly greater for high-taste, sweet, and salty foods, than for other food types. The patients cannot be characterized as showing carbohydrate craving, because sweet and starches are differentially preferred; nor can they be described as craving "forbidden" foods because red meats are restricted but not craved. The study inferred that craving for "high taste food" in NIDDM patients might result from diminished taste sensitivity or from highly restricted intake of sugar and salt.

The second study, the cognitive function in NIDDM, attempts to clarify whether patients with NIDDM also exhibit cognitive dysfunction. This study tests the hypotheses that: (l) Adults with NIDDM perform more poorly than matched controls on tests of verbal and visual recall memory, mental sequencing, and problem solving, but not on tests of immediate or recognition memory; (2) The magnitude of impairment is greater for patients in poor metabolic control than in good control; and, (3) Differences between NIDDM patients and controls persist after controlling for differences in depression and anxiety.

NCRR's Comparative Medicine Program recently supported a test of taurine as an essential nutrient in primates. The amino acid taurine is an essential nutrient for normal retinal and brain development in cats, but its importance in primates is less well defined. Human infants fed low-taurine infant formulas have low blood levels of taurine compared to infants fed human milk, which is very rich in taurine, and children maintained on taurine-free parenteral nutrition show electroretinographic and ophthalmoscopic abnormalities. Researchers at the Oregon Regional Primate Research Center are studying dietary taurine deficiency in rhesus monkeys in order to define its biochemical, morphological, and functional effects and their timing and reversibility.

From birth, rhesus infants were fed a taurine-free human infant formula and compared to infants fed the same formula supplemented with taurine. The investigators have previously showed that taurine levels in plasma were reduced by approximately 50 percent in taurine-deprived monkeys at 3 and 6 months of age, as in human infants fed similar formulas, and that their visual acuity was subnormal at 1-3 months. Taurine-deprived monkeys showed abnormal retinal morphology, particularly in cones in the foveal region. However, the changes were less severe at 6 than 3 months, suggesting a spontaneous decrease with age. This hypothesis has been confirmed by new results for 12-month-old monkeys, which showed further lessening of ultrastructural retinal defects and normalization of plasma and retinal taurine levels. However, even if effects on the retina regress spontaneously, their distortion of visual input during critical early postnatal months may induce irreversible effects on the visual cortex. At 1-3 months, changes were found in cortical evoked responses to visual stimuli. At both 3 and 6 months, the visual cortex of deficient monkeys showed shifts in the laminar distribution of neurons and poor neuronal differentiation and arborization. The researchers plan to confirm these cortical differences by quantitative morphometry, follow their progression at 12 and 24 months of age, and determine whether they occur only in visual areas of cortex. They will also assess effects of taurine deprivation on auditory function, learning, and memory.

The intramural Veterinary Resources Program at NCRR has undertaken a study of two different lipoprotein phenotypes in the Watanabe Heritable Hyperlipidemic (WHHL) rabbit. Current evidence suggests that WHHL rabbits, which have an LDL receptor defect, can be classified into two types: type 1, those with premature coronary atherosclerosis, and type 2, those with slow development of coronary atherosclerosis. Both types of WHHL rabbits are characterized by high cholesterol and triglyceride concentrations. Electrophoretic analysis of the sera from the two types of rabbits showed a distinct difference in their VLDL fraction. These are significant findings and, therefore, a sensitive agarose gel electrophoretic technique was used to determine the sera lipoprotein electrophoretic patterns of WHHL rabbits from the National Institutes of Health. The results showed two distinct phenotypes: one with an increased density of beta-lipoprotein and another with a beta-doublet. When these are compared to human phenotypes, the phenotype with the increased density of beta-lipoprotein resembles type II hyperlipoproteinemia. The results of this study indicate that the WHHL rabbits with the beta-doublet lipoprotein phenotype and type 1 WHHL rabbits have similar VLDL characteristics. The beta-doublet and beta-VLDL lipoprotein phenotypes are associated with defective apolipoprotein E. Some apolipoprotein E defects are related to increased risk of coronary artery disease. However, the risk can be reduced significantly by diet. Therefore, the apolipoprotein phenotypes of the WHHL rabbits will be characterized, and the possibility of dietary intervention as a means to improve the husbandry of these rabbits will be investigated.

HIGHLIGHTS OF NUTRITION RESEARCH: NATIONAL NUTRITION MONITORING

The National Nutrition Monitoring System includes all Federal surveys and surveillance activities designed to collect health and nutritional status measurements, food and nutrient consumption measurements, food composition measurements, dietary knowledge and attitude assessments, and food supply determinations. The NIH provides direct support to a variety of national nutrition monitoring activities, as well as supporting the science base that undergirds much of the monitoring system. Some examples of NIH contributions to national nutrition monitoring research are cited below.

Health and Nutrition Examination Surveys

To assess the nutritional status of Americans, particularly as related to health and mortality outcomes, a series of National Health and Nutrition Examination Surveys (NHANES) was begun in 1971. Conducted during 1971 through 1974 and 1976 through 1980, respectively, NHANES I and II constituted the largest in-depth national surveys, until now, of health and nutrition ever made on representative samples of the U.S. population. NHANES III, scheduled to run from 1988 through 1994, will provide much-needed updating of this critical information. Conducted by the National Center for Health Statistics (NCHS), the NHANES consists of a series of surveys of probability samples of the population, each comprising over 20,000 U.S. residents. The surveys include physical examination, anthropometry, blood cell assessments, biochemical analyses of blood and urine, x-rays, functional assessments, health histories, and dietary intake interviews. The resulting data provide national estimates of diseases and of health and nutritional characteristics of the U.S. population and selected subgroups. Additionally, NHANES I respondents have been traced and reexamined in a longitudinal followup study; information on decedents was obtained from hospital records, the National Death Index, and death certificates.

NHANES III also has been planned as a longitudinal study with morbidity and mortality end points. The survey will "oversample" older persons. (That is, approximately 7,000 persons aged 60 years and older will be included; of this group, about 1,000 will be aged 80 and older.) For the first time, NHANES III is collecting health and dietary information on the very old (age 75 and older), yielding a comprehensive resource for aging research. Blacks, Mexican Americans, and Puerto Ricans will be heavily represented in the general survey.

In addition to the national surveys, the NCHS conducted the Hispanic Health and Nutrition Examination Survey (HHANES) in 1982 through 1984. The HHANES, which included assessments like those of the NHANES, was a population-based survey of the health of three Hispanic groups in the United States: Mexican Americans in five southwestern states, Cuban Americans in southern Florida, and Puerto Ricans in the New York City metropolitan area.

The NIH supports HANES in several ways. NIH-supported scientists participate in the planning of each HANES survey. The NIH devotes research funds to improving methods and techniques of measuring dietary intake, to fine-tuning biochemical and clinical indices of nutritional status, and to perfecting other assessment and monitoring parameters. Each year NIH institutes fully or partially support HANES followup surveys. During the years of the survey itself, NIH institutes fund both the survey and followup activity.

Eight NIH institutes (NCI, NHLBI, NICHD, NIDR, NIDDK, NIAID, NIA, and NIAMS) contribute to HANES regularly. For example, the NIA is collaborating with the NCHS to fund acquisition of additional dietary intake information and collection of health and dietary information on a longitudinal basis from older participants. The NHLBI is funding lipoprotein analysis and survey measurements that assess cardiovascular risk factors. The NICHD supports methodology to investigate growth relationships and dietary intake. The NIAMS supports aspects of the survey related to arthritis, osteoporosis, and skin diseases. The NIDDK funds measurements related to gallstones, kidney disease, and diabetes. The NIDR continues to fund the oral health examination and questionnaire component.

The NIA, in a cooperative agreement with the NCHS, initiated a follow-back study of the NHANES III to collect additional nutrition data from the survey respondents over 60 years of age. Two additional 24-hour food intake recalls are obtained by telephone in addition to the in-person interviews obtained in the NHANES Survey. Recalls from 2 weekdays and one weekend are collected from each respondent at regular intervals over a year. The first year's data have been collected, and analysis of dietary intake is underway at the GRC. The computerized dietary intake interview system used by the NHANES III has been installed at the GRC, making it possible to compare data from the Baltimore Longitudinal Study of Aging (BLSA) with the NHANES III.

The Heart, Lung, and Blood Supplement to the NHANES III affords an opportunity to augment existing knowledge of the prevalence and distribution of these diseases by developing an additional component to the NCHS core exam. This component of additional questions and procedures will provide information on common heart, lung, vascular, and blood diseases, risk factors, and elements of medical care. It will indicate how representative NHLBI population-based epidemiological studies are and to what extent the findings of these studies may be generalized to the U.S. population.

The NIH derives significant research advantages from HANES data. Various institutes perform followup studies using HANES data to test hypotheses about the relationship of dietary practices to the incidence of cancer, heart disease, obesity, osteoporosis, and kidney disease, as well as to assess diets and to study the effect of diet on overall health and longevity. Extramural researchers supported by NIH also make extensive use of HANES data. For example, researchers are currently using HANES data in the conduct of studies on:

- The impact of living arrangements on dietary status in U.S. adults.
- The proximate determinants and their associated biosocial and biobehavioral roots of low birth weight and infant mortality in black, white, and Hispanic women.
- Secular trends in cardiovascular risk factors in the adolescent and adult U.S. population.
- The relationship of smoking and body weight, including evaluation of the independent and additive or synergistic contribution of smoking rate and fasting glucose on body weight.
- The strengths and weaknesses of dietary measures of alcohol consumption in epidemiological studies of alcohol as a risk factor for chronic disease.
- The relation of chemopreventive, nutritional, and constitutional factors to cancer.
- The relationship of marital status and obesity.

Other NIH-supported Nutrition Surveys

In addition to the HANES series, the NIH supports or undertakes other valuable nutrition surveillance efforts. The following are a few recent examples:

- Cholesterol Awareness Surveys (NHLBI and FDA), conducted among physicians and other U.S. adults in 1990.
- Nationwide Survey of Nurses' and Dietitians' Knowledge, Attitudes and Behavior Regarding Cardiovascular Risk Factors (NHLBI), conducted in 1990.
- Basic Office of Cancer Communications National Knowledge, Attitude, and Behavior Survey (NCI), 1988-1991.

Methodology for Nutrition Assessment

NIH supported studies on methodologies for nutritional and dietary assessment include:

- Assessment of nutritional anemias.
- Evaluation of selenium status.
- Indices of biotin nutritional status.
- Measures of tissue and blood levels of carotenoids.

Recent activities in this research area are summarized below.

- Methodologic research relevant to studies of nutrition and cancer is being carried out by NCI in conjunction with the National Institute of Standards and Technology (NIST). Both prospective and retrospective studies have consistently demonstrated that consumption of vegetables and fruits reduces the risk of lung cancer and possibly other cancers. Beta-carotene is a likely protective factor, but other carotenoids share its antioxidant ability and have not been adequately investigated. A high-performance liquid chromatographic method that quantitatively recovers and measures the major carotenoids in human serum has been developed and will permit a comparative investigation of individual carotenoids in sera stored in prospective studies.

- Although vitamin C has been postulated to play a role in cancer risk, it has rarely been investigated because of its instability in serum samples. Methods to protect it at the time of blood collection and during long-term storage have been developed and validated. Studies are now focusing on stabilizing and measuring the oxidized (inactive) and reduced (active) forms of vitamin C in human serum.

- As body fat distribution has been recognized as a disease risk factor, practical methods for the measurement of body girths are needed. In two groups of postmenopausal women aged 55-69 years in the upper Midwest, the reliability and accuracy of self measurement by mail questionnaire of waist, hip, upper arm, wrist, and calf girths was examined. Intraclass correlations for waist girth was 0.96 when comparing two self measurements, and 0.93 when comparing self with technician measurement. Other intraclass correlations were at least 0.85 for repeat self measurement except for wrist, which had an intraclass correlation of 0.66. For comparisons of self with technician measurement, intraclass correlations ranged from 0.71 for upper arm to 0.98 for hips. There was slight overestimation of waist girths and underestimation of hip girths, comparing self with technician measurement. Accuracy of self measurement did not seem to vary according to age or educational status, but for hip, wrist, and calf girths it appeared that self measurement underestimated technician measurement as girth increased. For most girths, within-person variation in girth measurement also increased as girth size increased. Overall, girth self measurement was both repeatable when reascertained by mail and accurate when compared with subsequent technician measurement.

- Long-term dietary observational and intervention studies demand accurate and reliable measurement of subjects' diets. A new research initiative has been designed by NCI to identify and establish a network of institutions or organizations with scientific expertise, facilities, and capabilities to conduct the variety of studies necessary to develop markers of dietary adherence. Included in such studies are, for example, controlled feeding studies, metabolic studies, and field studies to identify, characterize, and evaluate biochemical and biological markers of dietary adherence. NCI expects these studies to emphasize dietary patterns that include reduced levels of total fat and saturated fat, increased levels of complex carbohydrates and fiber, and also will include a variety of foods typically present in the United States diet. The studies also will vary the level of fat intake, while keeping fiber intake constant, so that weight loss and energy balance will be addressed.

Food Composition Methodology

In order to fill potential gaps in the information provided by other agencies, several NIH institutes undertake studies which include analysis of the nutritional content of food. A few such examples include:

- Dietary fiber and fiber components, carotenoids, vitamin A, and selenium analyses (NCI).
- Taurine, pyridoxine beta glucoside, molybdenum, and biotin analyses (NIDDK).
- Development of methods for determining nutrients in human colostrum and milk (NICHD).
- Mutagens from the cooking of foods (NIEHS).
- Food fatty acid analysis and evaluation (NHLBI).
- USDA Services for Nutrient Composition Laboratory (NHLBI). This interagency agreement supports the development of new or improved techniques for the analysis of nutrients, especially lipids, carbohydrate fractions, trace minerals, and amino acids.

Computerized Nutrient Data Sources

Examples of NIH-supported nutrient data bases include the following:

- USDA Nutrient Data Bank. The NHLBI supports the continued development of the USDA Nutrient Data Bank and the USDA revision of Agriculture Handbook No. 8, *Composition of Foods: Raw, Processed, Prepared*. Funds are specifically directed to the compilation of accurate food composition data for nutrients associated with heart, lung, and blood diseases (lipids, carbohydrate fractions, trace elements, and amino acids).
- Nutrition Coordinating Center. The NHLBI supports a standardized system at the University of Minnesota for collecting, coding, processing, and analyzing dietary information. The information in the interactive computer data base comes from the USDA, other standard references, and food manufacturers. The coding manual and nutrient data base are continually updated by a staff of nutritionists and data specialists to reflect changes in the marketplace. This system has been field tested extensively in studies throughout North America since 1974.

HIGHLIGHTS OF TECHNOLOGY TRANSFER ACTIVITIES

The National High Blood Pressure Education Program (NHBPEP)

The NHBPEP, begun by NHLBI in 1972, is a major comprehensive effort aimed at reducing morbidity and mortality associated with hypertension. Lifestyle and behavior changes have been the cornerstone of the NHBPEP. In FY 1990, working group reports were prepared on such topics as hypertension in pregnancy, the management of patients with hypertension and high blood cholesterol, hypertension and chronic renal failure, and ambulatory blood pressure monitoring. An emphasis of the National High Blood Pressure Education Month campaign in May 1990 was on the relationship between high blood pressure and stroke, especially in the Stroke Belt states--11 states, mostly in the southeastern United States, that have higher than average age-adjusted death rates from stroke. The release of new radio and television public service announcements and the celebration of the first Sunday in May as Church High Blood Pressure Sunday were components of the campaign. The NHBPEP Stroke Belt Initiative, which began in May 1990, is refocusing and increasing efforts toward reducing stroke morbidity and mortality in the Stroke Belt states through three components: outreach through churches, a mass media campaign, and funding to stimulate the development of innovative educational strategies. Some of these strategies address the issues of weight control, sodium restriction, and smoking cessation.

The National Cholesterol Education Program (NCEP)

Since its initiation in 1985 by NHLBI, the NCEP has made substantial contributions to the successful nationwide campaign to raise professional and public awareness of the importance of lowering high blood cholesterol levels. A major event for the NCEP in FY 1990 was publication of the *Report of the Expert Panel on Population Strategies for Blood Cholesterol Reduction*. The report makes recommendations to help healthy Americans adopt eating patterns to lower blood cholesterol levels and risk of CHD. The report addresses individuals, special population groups, health professionals, the food industry, relevant government agencies, mass media, and education systems. Building on this document, the Expert Panel on Blood Cholesterol Levels in Children and Adolescents continued development of its report designed to encourage all young people to adopt heart-healthy eating patterns and to offer recommendations for detecting and treating high blood cholesterol in children and adolescents.

Another NCEP panel report, *The Laboratory Standardization Panel Recommendations for Improving Cholesterol Measurements*, was also published in 1990. This report provided recommendations to all clinical laboratories to improve the accuracy and precision of cholesterol measurement.

In 1990, a nursing education program was initiated to educate registered nurses about the identification, treatment, and counseling of patients with elevated blood cholesterol. It was cosponsored by NHLBI, the American Heart Association, the American Nurses Association, the Black Nurses Association, and NCNR.

September 1990 marked the second annual National Cholesterol Education Month and the beginning of a new mass media campaign that emphasizes the importance of each individual knowing his or her blood cholesterol level and taking action to control it by eating foods low in saturated fat, total fat, and cholesterol. A continuation and expansion of the successful "Stay Young at Heart Program" was featured for National Cholesterol Education Month at the NIH. This nutrition education point-of-purchase program, originally introduced at NIH in 1987, involves the use of 11 recipes that originated in the Multiple Risk Factor Intervention Trial and Coronary Primary Prevention Trial which are lower in saturated fat, cholesterol, and sodium, as well as various other useful materials (recipe cards, dispenser, apron, button, poster, tent cards, evaluation card, and flyer). Additional recipes and a new poster were highlights of the program in 1990. Its success at the NIH cafeterias has led to its implementation in a variety of settings.

To help planners and educators increase health promotion programs in such areas as high blood pressure, cholesterol, and smoking, *NHLBI Kit '90: The Right Moves* was prepared. It consists of a two-manual collection of ideas, educational materials, and information, including reproducible pieces and reference tools. Other publications released in FY 1990 include *Facts About Blood Cholesterol,* a revised fact sheet that reflects the NCEP's population recommendations for a low-saturated fat, low-cholesterol eating pattern, and *Eating Right to Lower Your High Blood Cholesterol,* a patient education brochure written for readers at lower reading levels who have high blood cholesterol.

The NHLBI sponsored national telephone surveys of practicing physicians and the adult public in 1983, 1986, and 1990 to assess attitudes and practices regarding high serum cholesterol levels. Trends show continuing change in medical practice and public health behavior related to serum cholesterol. In 1990, physicians reported treating serum cholesterol at considerably lower levels than in 1986 and 1983. The number of adults who reported having had their cholesterol level checked rose from 35 to 46 to 65 percent in 1983, 1986, and 1990. In 1990, 90 percent of physicians reported awareness and use of the *Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults,* and the public reported marked increases in awareness of dietary methods to lower blood cholesterol.

NIDDK National Task Force on Prevention and Treatment of Obesity

The NIDDK has created a National Task Force on Prevention and Treatment of Obesity. The first objective of the task force will be to synthesize current, scientifically-based information about obesity through the development of summary documents on a series of important issues related to its prevention and treatment. These summary findings will then be disseminated by the NIDDK through its Office of Health Research Reports, through its National Information Clearinghouses, through the submission of articles for publication in scientific journals, or through other means.

The second objective of the task force will be to identify concepts for possible future clinical research studies in obesity. The overall goal of the NIDDK is to effect the transfer of information underpinned by a strong scientific foundation to benefit the American public in the prevention and treatment of obesity.

NHLBI Obesity Education Initiative

Late January 1991, the NHLBI began a new education initiative on obesity which will be coordinated out of the Office of Prevention, Education and Control (OPEC). Because obesity impacts upon many cardiovascular risk factors, as well as independently affecting cardiovascular disease, the institute decided to begin a more concerted effort to educate the public and health professionals of these relationships.

Up to now, the issue of obesity has been addressed as it relates to high blood cholesterol, high blood pressure, and smoking through the existing National Cholesterol Education Program, National High Blood Pressure Education Program, and the NHLBI Smoking Education Program. The issue of obesity in minority populations has been of interest to the NHLBI *Ad Hoc* Committee on Minority Populations. The NHLBI Obesity Education initiative will formalize all education activities related to obesity in order to enhance and integrate the many issues related to obesity and its relationship to cardiovascular disease.

The model to implement the initiative will include:

A) A task force of representatives from the appropriate NHLBI Divisions, OPEC, and possibly experts from academia. It would consider the various scientific issues related to obesity's relationship to cardiovascular disease, identify issues where consensus opinions can and should be reached, convene expert *ad hoc* advisory panels to address certain issues, and recommend the types of educational messages which should be brought to the public and to professionals in order to help reduce the prevalence of obesity.

B) The *ad hoc* advisory panels would consist of appropriate task force members and outside experts knowledgeable of particular areas who would be called together to address very specific issues. Selected advisors from various organizations dealing with professional and public education issues would be integrated on the advisory panels in order to help assure the dissemination of the information to the appropriate audiences through the appropriate channels.

Nutrition and Oral Health

In the September 1990 NIDR publication *Broadening the Scope, Long-Range Research Plan for the Nineties* (NIH Publication No. 90-1188), the NIDR has reported on new findings and new directions in subject areas devoted to nutrition and diet and to fluorides. Nutrition initiatives also are found in several of the nine other sections in the volume.

Water Fluoridation

The safety and efficacy of water fluoridation have been confirmed following an exhaustive review of human and animal data by an expert committee convened by the Assistant Secretary for Health. The study was ordered following release of data by the National Toxicology Program of the NIEHS that fluoride in very high doses might be associated with the development of osteosarcomas in a small number of experimental animals. The committee's conclusions were published in 1991 in the publication, *Review of Fluoride: Benefits and Risks.*

Not only was no evidence found of an association between fluoride and cancer in humans, but the committee confirmed that fluoride plays a central role in preventing tooth decay, thereby reducing abscesses and extractions and providing "improved health" to all, "especially poor children." The committee recommended research in several areas, including those related to the systemic effects of fluoride on teeth and bones.

Cancer Prevention Outreach to State and Local Health Departments

The NCI has recognized the critical role of public health agencies in cancer prevention and control and has developed a research and publications program to support public health agencies in their cancer control efforts. State and local health departments form a national infrastructure through which cancer prevention and control efforts may be addressed. They have the statutory responsibility for the health of the community, provide direct health service to a significant part of the population, have a particular orientation to the health needs of underserved populations who may have a higher than average risk and poorer experience, and are experienced in working with a broad range of community groups and agencies.

Since 1987, NCI has funded 21 states plus Los Angeles County and the District of Columbia to build their cancer control capacity or utilize existing data resources to develop a state cancer plan and to initiate interventions based on that plan. In addition, NCI staff has provided technical assistance in such areas as planning, program development, and data and registry improvement. Monthly mailings of materials related to cancer prevention and control are sent to each of the 50 state health departments and the District of Columbia. In addition, NCI staff collaborate with representatives from states across the country to produce reports for guiding public health agency activities, for developing state tobacco prevention and control plans, and for screening mammography. The resulting reports have been disseminated to key cancer control individuals in every state.

Community-based Risk Reduction Research Demonstration Studies

The NHLBI is funding three investigator-initiated community-based research and demonstration programs designed to reduce risk of CVD through a population-wide approach to primary disease prevention. By multiple education and evaluation strategies, the programs help communities choose and practice more healthy behaviors and enhance community efforts to support these behaviors. The oldest project is the Five-City Project in California at Stanford University Medical School, and the others are the Minnesota Heart Health Program located in the School of Public Health at the University of Minnesota and the Pawtucket Heart Health Program based at Memorial Hospital in Rhode Island and affiliated with Brown University.

The three projects were established to develop and assess the effectiveness of community-based programs to prevent atherosclerotic heart disease by modifying behaviors and therefore risk factors that contribute to the development of this disease. The specific risk factor targets include smoking, cholesterol-elevating diets, high blood pressure, obesity, and physical inactivity.

The major aim of the studies is to test the hypothesis that a significant decrease in the multiple logistic risk for the educated communities will lead to a decline in morbidity and mortality from cardiovascular disease beyond that attributable to the secular trend. All of the studies are using multidisciplinary research teams, multiple models of community organization, multiple education strategies, and multiple evaluation strategies, including cross-sectional and cohort surveys and morbidity and mortality surveillance.

The Stanford Five City Project is in the 13th year of a 14-year study. The project began in 1978. The study involves two intervention communities and three control communities. The Minnesota Heart Health Program is a 13-year research study that began in 1980 and currently is in its 11th year. The education campaigns are staged successively in three communities that are matched with control communities. The paired communities included two small towns, two large cities, and two suburban areas. The Pawtucket Heart Health Program is a 15-year study that began in 1980 and is currently in its 11th year. There is one intervention and one matched control community.

The major results paper for the Stanford study reported that significant net reductions in community averages favoring treatment occurred in plasma cholesterol level (2 percent), blood pressure (4 percent), resting pulse rate (3 percent), and smoking rate (13 percent) of the cohort sample. These risk factor changes resulted in decreases in composite total mortality risk scores (15 percent) and CHD scores (16 percent). In addition, there were changes in knowledge about risk factors. The Minnesota Heart Health Program has completed the interventions and final cross-sectional and cohort surveys. The Pawtucket Heart Health Program will complete interventions by mid-1991. The final cross-sectional and cohort surveys need to be conducted.

Worksetting Cardiovascular Disease Research Studies

With increased interest in the worksetting for disease prevention and health promotion, the NHLBI Division of Epidemiology and Clinical Applications continues support of research on interventions for CVD risk factor reduction at the worksite. Efforts directed toward high blood pressure control among male employees in white-collar settings have been generally successful. Currently funded projects seek to extend worksite programs to other risk factors (smoking, weight control, cholesterol reduction) and to reach blue-collar and minority workers.

Ongoing projects include a program for employees in a large Southern city; smoking cessation and obesity control programs located in 30 medium-sized firms to test different types of incentives for risk factor reduction; a project to hasten return to work after coronary bypass surgery; smoking cessation programs using different strategies compared among 60 firms; and diet change and smoking cessation compared across 26 firms with varying organizational characteristics. These projects are the research complement to other ongoing programs under the NHLBI Workplace Initiative of the Office of Prevention, Education and Control, which has responsibility for technology transfer and publications related to worksite disease prevention and health promotion.

Child and Adolescent Trial of Cardiovascular Health (CATCH)

The overall goal of CATCH is to measure and compare the effects of school-based interventions for promoting long-term healthful behavior in elementary school children and adolescents to reduce their subsequent cardiovascular disease risk. The school-based interventions include classroom curricula, family- and home-based education, and school environmental modifications related to food consumption, physical activity, and tobacco use.

For the main trial, schools will be randomly assigned to one of three conditions: control, curriculum plus environmental changes, or curriculum plus environmental changes plus parental involvement. The primary outcome measure is change in total serum cholesterol. Other outcomes will include systolic blood pressure, physical activity levels, non-use of tobacco, level of total fat and sodium consumption, and consumption of unsaturated fat and complex carbohydrates. There were 8 schools and 1,400 children in the Feasibility Study. A total of 96 schools located in California, Louisiana, Minnesota, and Texas will be involved in the main trial. A cohort of approximately 12,000 students will enter as third graders and be followed through fifth grade.

School-based Cardiovascular Health Promotion and Disease Prevention Program

The NHLBI currently funds a number of school-based cardiovascular risk reduction studies that are categorized as demonstration and education research. Most of the study designs involve randomization of schools to treatment and control conditions with pre-post repeated measures. Multidisciplinary research teams address one or more of the following risk factors: nutrition, exercise, smoking, high blood pressure, and stress.

Outcomes that are being measured include knowledge, attitudes, behavior, and physiological measures. Several of the studies focus on school policy and procedure changes related to school cafeteria food content and preparation and physical activity opportunities for children. The grade levels range from 3rd to 10th. Some of the projects have a family or parent component to the study. In a large number of the studies, major racial and ethnic minorities comprise the study populations. Several new studies will address the effectiveness of teacher training on student outcomes.

Cuidando Su Corazón: Weight Reduction for Mexican Americans

The purpose of the demonstration and evaluation project, "Cuidando Su Corazón," at Baylor College of Medicine in Houston, is to develop and assess the effectiveness of a culturally sensitive program to help young Mexican-American families lose weight and reduce their risk of cardiovascular disease by adopting a low-fat diet and a regular exercise program.

Nutrient information is available for a subsample of female subjects who completed baseline, 6-month, and 12-month measurements. Overall, at baseline, the energy intake of women was 1,694 calories per day, and protein, fat, and carbohydrate contributed 16, 38, and 45 percent of calories, respectively. At 12 months, evidence that the research intervention designed to promote weight reduction had produced some effect was reflected in a reduced caloric intake of 1,308 calories per day and a redistribution of calories so that 17 percent came from protein, 34 percent from fat, and 47 percent from carbohydrate.

Analysis of available weight data indicates that people in both intervention groups (tailored to the individual and tailored to the family) lost weight during the program, and were able to maintain this loss for up to 1 year. The family group lost slightly more weight than the individual group, with more people losing weight and fewer gaining or maintaining initial weight during the program. Contrary to the original hypothesis, there was no relationship between weight loss and any of the other measures of cardiovascular risk, including cholesterol (total-, HDL-, or LDL-cholesterol), blood pressure, or plasma glucose level. The lack of effect of weight loss on these measures may have been due to the fact that baseline values for each of these measures were well within the range of healthy scores and lower than the national average. This is not surprising because the study was purposefully designed to recruit a young (18-45 years old) healthy group and to exclude diabetic, hypertensive, and hyperlipidemic individuals.

Cancer and Nutrition School Curricula Development

A joint effort between the NCI and the American Cancer Society has resulted in the development of intermediate and secondary school curricula on nutrition education to lower cancer risk. The curricula have been disseminated to the American Cancer Society divisions to be made available to schools throughout the United States. A companion effort to the curriculum was the development of a guide for school food service managers.

HIGHLIGHTS OF TRAINING PROGRAMS WITH NUTRITION COMPONENTS

The principal mechanisms for NIH support of training programs in biomedical and behavioral nutrition research are the extramural institutional and individual awards. The institutional awards, called "training grants," enable institutions to make training awards to individuals they select for predoctoral and postdoctoral research training. In FY 1990, NHLBI, NIDDK, NIGMS, NICHD, NCI, and NIDR supported such institutional training grants in nutrition. Individual awards, called "fellowships," in nutrition include predoctoral and postdoctoral individual national research service awards and international research fellowships that permit recipients to broaden their scientific backgrounds and extend their potential for research in nutrition. Individual nutrition fellowships were supported in FY 1990 by NIDDK, NICHD, NCNR, FIC, NIAID, NICHD, NIAMS, and NHLBI. Selected highlights of these and other training programs with nutrition components are presented below.

Research Training and Career Development Awards in Nutrition and Obesity

The Nutritional Sciences Program of the Division of Digestive Diseases and Nutrition (DDDN), NIDDK, supports research, research training, and career development programs on nutrient metabolism, obesity, eating disorders, and energy regulation. NICHD supports similar activities in the nutrition of low birth weight infants, nutrient metabolism as related to growth and development, nutritional antecedents of adult disease, and dietary therapy of inborn errors of metabolism. Nutrition- and obesity-related research needs and opportunities in the early decades of the next century will require an increased number of physicians and basic scientists with nutrition sciences training that can be related to clinical nutrition problems falling within the DDDN and NICHD program areas. The number of awards for training support aimed at supplying this cohort of qualified scientists has declined over the past decade. Thus, an increased effort has been directed to strengthening the national capacity for nutrition- and obesity-related research. The intent is to provide research training and career development support to persons who have a commitment to and an aptitude for research in nutrient metabolism, obesity, eating disorders, and/or energy regulation, as well as maternal-fetal, infant, and childhood nutrition.

Preventive Cardiology Academic Award Program

The Preventive Cardiology Academic Award (PCAA), supported by NHLBI, is a 5-year award made to successful applicant schools of medicine and osteopathy throughout the United States. The award is designed to foster initiation of and improvement in preventive cardiology curricula and to stimulate research and careers in the area of primary prevention of cardiovascular disease. An annual meeting of the awardees is held each April in Bethesda to facilitate networking and collaborative activities among the awardees.

Fifty-four medical schools have been or are currently involved in the PCAA program. There are 22 current awardees. Thirty-two institutions have completed their awards. The first awards were made in 1979 with a new class starting each subsequent year. The 13th and last PCAA program announcement was released in November 1989. It focused on minority health and physician training. The last class of six began July 1, 1991.

Cardiovascular Disease Nutrition Teaching Aids for Medical Students, Physicians, and Allied Health Professionals

The long-term objective of this NHLBI program is to enhance the teaching of nutrition in relation to CVD in medical schools with the ultimate goal of improving the prevention, treatment, and control of CVD. The major objective of phase I of this SBIR project was the development of computerized and hard-copy catalogues of the various teaching aids available to teach nutrition and CVD to medical students and practicing physicians, as well as other health professionals.

The phase II project developed a computer-assisted instruction program in the form of an interactive videodisc (IVD). The IVD will provide a self-paced course for medical students and physicians on CVD risk factor appraisal and the nutritional management of patients with dyslipoproteinemias. Both the catalogue from phase I and the subsequent nutrition teaching aids to be developed in phase II will have market value.

Phase I has been completed, with plans underway for marketing the computerized catalogue. Phase II began September 30, 1988. In phase II, four patient case scenarios were developed and the formative evaluation completed. The summative evaluation is being carried out in four medical schools with 120 junior and senior medical students.

In phase I, materials were analyzed, assessed for accuracy and quality, and indexed by media. The availability of various teaching aids for the major CVD nutrition subject areas was determined, needs identified, and a plan prepared to meet certain of these needs in a phase II project. During phase I, a demonstration module for an IVD also was developed.

NIGMS Trauma and Burn Injury Research Training

The Trauma and Burn Injury Program area of the NIGMS supports research training related to the underlying mechanisms of the body's systemic responses to traumatic injury through the awarding of Individual and Institutional Postdoctoral National Research Service Award (NRSA) grants. The goal of these efforts is to improve the understanding of the body's response to major injury and to foster the more rapid application of this knowledge to the treatment of trauma and burn-injured victims. Trainees, most of whom hold the M.D. degree, are expected to spend at least 2 years in the training program and to apply such basic disciplines as biochemistry, physiology, immunology, microbiology, cell biology, molecular biology, biomedical engineering, or behavioral sciences to the study of trauma. Currently, there are more than 45 NRSA postdoctoral trainees supported by this program, and a research focus that is being actively pursued is the role of nutritional status in the management of trauma.

NCI Cancer Prevention Fellowship Program

The Cancer Prevention Fellowship Program is a 2- to 3-year training program designed to prepare physicians and scientists from a variety of appropriate disciplines (e.g., public health, behavioral or nutritional sciences) for a career in cancer prevention research and application. The program has three major components: participation in an academic course designed to give trainees basic concepts and skills in cancer prevention; research experience at the NCI working with individual preceptors selected from senior program and research staff; and brief field assignments at institutions outside the NIH involved in cancer prevention and control. Eligibility is limited to M.D. or Ph.D. candidates who are citizens or permanent residents of the United States.

Nutrition and Oral Health

The NIDR training program in nutrition and oral health at the University of Alabama, Birmingham is designed to provide both pre- and postdoctoral trainees with training leading to an M.S., M.P.H., or Ph.D. in nutrition, or Dr. P.H. in one of the interacting departments, namely Community and Public Health, the Research Center for Oral Biology, or the Department of Nutrition Sciences. The overall aim of the program is to provide training in nutrition relating to oral health so that trainees may become independent researchers and teachers in the area of nutrition with emphasis on oral health. Present trainees are doing research that includes: bone restoration by osteoinductive proteins; bone proteoglycan biochemistry and the effect of vitamin D on the proteoglycan metabolism; and analysis of salivary components in breast cancer patients.

Section 4. Financial Report of Biomedical Research and Training in Nutrition

FINANCIAL REPORT OF BIOMEDICAL RESEARCH AND TRAINING IN NUTRITION

THE LEADER IN FEDERALLY SUPPORTED NUTRITION RESEARCH AND TRAINING

In FY 1990, the NIH led all Federal agencies in financial support of nutrition research and training, for a total of $292 million. This total represents the combined individual contributions of the 13 NIH institutes and 3 centers that supported biomedical nutrition research and training. Actual obligations for FY 1990 biomedical nutrition research and training for all NIH ICDs as amounts and as percentages of their total obligations are shown in table 1. Leading the ICDs in total dollars expended in support of nutrition research were NIDDK, with $67.5 million; NCI, with $67.0 million; NHLBI, with $61.8 million; NICHD, with $28.9 million; and NCRR, with $23.0 million. Leading NIH components in terms of the percentage of total budget of each ICD dedicated to the support of nutrition research and training were NIDDK, with 11.6 percent; NICHD and NCRR with 6.5 percent; and NHLBI, with 5.8 percent.

Table 1. Actual Obligations, NIH Biomedical Nutrition Research and Training, as a Percentage of Total ICD Obligations, by NIH Component, FY 1990 (in thousands of dollars)

ICD	Nutrition Research and Training*	Total ICD Obligations**	Nutrition as Percentage of Total ICD Obligations
NCI	$66,987	$1,644,330	4.1
NHLBI	61,834	1,070,683	5.8
NIDR	1,787	135,432	1.3
NIDDK	67,526	579,984	11.6
NINDS	1,143	489,348	<1.0
NIAID	4,104	831,181	<1.0
NIGMS	2,285	680,305	<1.0
NICHD	28,857	441,955	6.5
NEI	8,957	236,456	3.8
NIEHS	8,641	228,725	3.8
NIA	10,070	238,927	4.2
NIAMS	4,362	168,538	2.6
NIDCD	1,974	117,283	1.7
NCRR	23,052	353,771	6.5
FIC	118	15,479	<1.0
NCNR	665	33,508	2.0
Total	$292,359	$7,325,432†	4.0

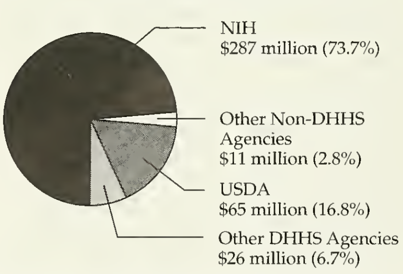
ICD = Institute/Center/Division
*Actual obligations. Source: Human Nutrition Research and Information Management (HNRIM) System data base.
**Obligations. Source: NIH Office of Program Planning and Evaluation.
† Total excludes obligations for Office of the Director, National Library of Medicine, and buildings and facilities.

TRENDS IN NUTRITION RESEARCH AND TRAINING, 1980-1990

In FY 1989, the NIH led all Federal agencies in financial support of nutrition research and training, with a FY 1989 total of $287 million, as shown in figure 3. This total represented 74 percent of all Federal expenditures and 92 percent of all DHHS expenditures in nutrition research and training. NIH expenditures have consistently represented between 70 and 74 percent of the total Federal expenditure and between 92 and 95 percent of the total DHHS expenditure in nutrition research and training.

NIH nutrition research and training dollars have steadily increased during the past decade, growing from $139 million in FY 1980 to $292 million in FY 1990. NIH actual obligations for nutrition research and training by NIH

Figure 3. Federal Expenditures in Support of Human Nutrition Research and Training, FY 1989



Source: Human Nutrition Research and Information Management (HNRIM) System data base.

Table 2. Actual Obligations, NIH Biomedical Nutrition Research and Training, by ICD, FY 1980-1990 (in thousands of dollars)

ICD	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990
NCI	$28,687	$30,313	$30,553	$37,336	$50,119	$45,199	$46,223	$52,691	$59,563	$64,524	$66,987
NHLBI	32,184	35,213	35,449	38,350	44,553	45,689	49,265	57,285	60,314	64,287	61,834
NIDR	1,648	1,503	1,529	2,072	1,419	1,795	1,211	1,836	1,486	1,571	1,787
NIADDK	26,457	30,906	26,981	33,332	35,969	45,951	—	—	—	—	—
NIDDK	—	—	—	—	—	—	44,697	54,737	60,156	63,955	67,526
NINCDS	2,837	1,559	2,839	2,547	2,652	2,949	2,158	3,367	3,221	—	—
NINDS	—	—	—	—	—	—	—	—	—	1,095	1,143
NIAID	1,047	1,562	1,853	1,606	1,646	1,679	1,830	2,652	3,493	3,797	4,104
NIGMS	2,451	2,503	1,841	2,081	2,271	2,307	2,291	2,710	2,529	1,953	2,285
NICHD	20,410	20,108	18,356	20,164	24,152	26,835	27,662	32,932	34,384	31,247	28,857
NEI	4,166	4,265	5,256	5,571	4,611	5,519	5,176	6,545	6,879	6,128	8,957
NIEHS	3,885	2,106	1,582	1,390	1,768	5,366	4,470	12,880	9,914	10,261	8,641
NIA	4,220	4,133	3,261	4,391	4,757	4,608	5,329	6,934	7,625	8,494	10,070
NIAMS	—	—	—	—	—	—	2,846	3,424	4,068	4,128	4,362
NIDCD	—	—	—	—	—	—	—	—	—	1,174	1,974
DRR	11,129	14,330	14,823	15,444	18,874	19,400	19,472	22,089	22,106	23,811	—
NCRR	—	—	—	—	—	—	—	—	—	—	23,052
FIC	—	—	—	22	127	19	56	57	30	92	118
NCNR	—	—	—	—	—	—	292	472	427	459	665
Total	$139,121	$148,501	$144,323	$164,306	$192,918	$207,316	$212,978	$260,611	$276,195	$286,975	$292,359

component during the past 11 years are shown in table 2. With a few exceptions, the trend in dollars has been steadily upward for all institutes, centers, and divisions.

As shown in table 3, total NIH expenditures for nutrition research and training have increased consistently since FY 1980 and have constituted approximately 4 percent of total NIH obligations during that time. Total NIH biomedical nutrition research and training support is shown in constant, as well as current dollars, in table 3. For example, nutrition research and training support showed a $153 million increase, or 110 percent, between FY 1980 and FY 1990 in current (unadjusted) dollars. In constant (adjusted) dollars (i.e., adjusted for inflationary price increases), however, nutrition and research training in FY 1990 represented a 17 percent increase over the FY 1980 level.

EXPENDITURES BY HNRIM SYSTEM CATEGORY AND INTEREST AREA

The NIH nutrition research support in the HNRIM System classification categories and the number of grants or contracts funded in each category are shown in table 4. The column labeled "actual obligations" represents the nutrition funding for projects in each classification category, not the funding for the classification category per se. For example, a study of the effects of smoking and diet on coronary heart disease and obesity that was considered to be 60 percent nutrition-related and had a total budget of $100,000 would contribute $60,000 towards the actual obligations reported for the area "Cardiovascular Disease and Nutrition" and $60,000 towards the actual obligations reported for the area "Obesity, Anorexia, and Appetite Control." The column labeled "percent of total"

Table 3. Actual Obligations, NIH Biomedical Nutrition Research and Training, in Current and Constant Dollars, and as a Percentage of Total NIH Obligations, FY 1980-1990 (in thousands of dollars)

Fiscal Year	Nutrition Research and Training, Current $	Nutrition Research and Training, Constant $*	Total NIH Obligations**	Current Nutrition $ as a Percentage of Total NIH Obligations
1980	139,121	139,121	3,428,842	4.1
1981	148,501	135,358	3,572,506	4.2
1982	144,323	121,178	3,643,461	4.0
1983	164,306	130,185	4,013,135	4.1
1984	192,918	144,508	4,493,553	4.3
1985	207,316	147,777	5,121,557	4.0
1986	212,978	145,766	5,296,977	4.0
1987	260,611	169,173	6,175,038	4.2
1988	276,195	170,691	6,610,430	4.2
1989	286,975	168,591	7,157,978	4.0
1990	292,359	162,521	7,581,484	3.9

*Based on biomedical R&D price index, FY 1980=100%. Source: NIH Data Book, 1990, NIH Publication No. 90-1261, September 1990.

**Source: NIH Data Book, 1990. NIH Publication No. 90-1261, September 1990.

represents the nutrition funds expended in a given category in relation to total NIH obligations for nutrition research and training, which totaled $292 million for FY 1990.

As illustrated in the example above, a grant or contract may appear in more than one category. Thus, if all actual obligations in the 41 categories were summed, the sum would exceed the total expenditures of $292 million.

Although NIH nutrition research encompasses all of the classification categories, the largest component is concentrated in the area of Research in the Biomedical and Behavioral Sciences (codes 1 through 25 and code 35). Codes 51 through 56 represent NIH Special Interest Areas.

SUPPORT BY EXTRAMURAL AND INTRAMURAL CATEGORIES

The NIH supports two broad categories of research: extramural and intramural. The extramural programs are responsible for roughly 90 percent of the total NIH resources in the form of research grants or contracts.

Through these programs, NIH makes awards of various kinds to institutions throughout the United States and the world. Extramural awards are based on a two-tiered peer-review assessment--one for scientific merit and one for program relevance.

Within the NIH itself, and accounting for approximately 11 percent of its budget, is the intramural program. All of the NIH institutes except NIGMS have an intramural component of laboratory and clinical research programs. More than 2,500 research projects are in progress at all times, making the NIH the largest center for biomedical and behavioral research in the world. Boards of scientific counselors are responsible for assessing the quality and direction of the intramural program, and the Office of the Director provides scientific and policy oversight.

The NIH relies on three major funding mechanisms as the administrative instruments

Table 4. Actual Obligations, NIH Biomedical Nutrition Research and Training, by HNRIM Classification Category, FY 1990

Nutrition Research Classification		Number of Grants and Contracts	Actual Obligations* (in thousands of dollars)	Percent of Total**
Code	Area			
1	Maternal Nutrition	149	18,732	6
2	Infant and Child Nutrition	250	38,632	13
3	Adolescent Nutrition	42	7,651	3
4	Adult Nutrition	78	12,372	4
5	Nutrition of the Elderly	103	15,899	5
6	Cardiovascular Disease and Nutrition	448	76,678	26
7	Cancer and Nutrition	518	73,375	25
8	Other Diseases and Nutrition	490	66,309	23
9	Trauma (Burns) and Nutrition	37	2,656	<1
10	Infection, Immunology, and Nutrition	133	18,781	6
11	Obesity, Anorexia, and Appetite Control	330	45,010	15
12	Genetics and Nutrition	149	22,740	8
13	Nutrition and Function	183	29,059	10
14	Nutrient-Nutrient/Drug/Toxicant Interactions	288	33,318	11
15	Other Conditions and Nutrition	434	52,539	18
16	Research on Nutritional Status	135	23,593	8
17	Carbohydrates	133	18,625	6
18	Lipids (Fats and Oils)	416	74,915	26
19	Alcohols	43	5,147	2
20	Proteins and Amino Acids	212	32,224	11
21	Vitamins	406	62,209	21
22	Minerals and Trace Elements	277	46,570	16
23	Water and Electrolytes	101	20,050	7
24	Fiber	26	5,766	2
25	Other Nutrients in Food	40	4,058	1
26	Food Composition	13	2,564	<1
27	Bioavailability	24	3,877	1
28	Effects of Technology on Foods/Diets	4	787	<1
29	Other Research in Food Service	6	501	<1
30	Food Consumption Surveys, R&D	10	1,868	<1
31	Research on Dietary Practices, Food Consumption, etc.	115	22,366	8
32	Methods for Educating and Informing the Public	36	11,409	4
33	Other Research in Nutrition Education	9	1,746	<1
34	Effects of Government Policy and Socioeconomic Factors	1	183	<1
35	Parenteral, Enteral, & Elemental Nutrition	77	12,802	4
51	Prevention of Disease	561	64,860	22
52	International Research	24	2,212	<1
53	Epidemiological Research	162	17,206	6
54	Education for Professionals	59	3,556	1
55	Education for the Public	34	6,871	2
56	Clinical Trials	139	33,818	12

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*The actual obligations represent the *nutrition* funding for projects in each classification area, not the funding for the classification area per se. A grant or contract may be assigned to more than one of these areás. Thus, summing the expenditures by area will yield a value that exceeds the total expenditures and summing the percent of total will yield a value greater than 100 percent.

**The total expenditure of the NIH nutrition program in FY 1990 was $292,359,000.

for accomplishing its program goals through the efforts of scientists outside the NIH (i.e., extramurally): grants and cooperative agreements (financial assistance awards) and contracts (acquisition awards). Appendix J gives details on NIH award mechanisms. Financial support by NIH of extramural nutrition research and training is provided through all three of these major funding mechanisms. Support of extramural nutrition research utilizes research project grants, program project grants, center grants, contracts, and cooperative agreements. All of these may include clinical trials; research resources support; reimbursement agreements; research career development awards; and new, academic, and teacher investigator awards. Extramural training in biomedical and behavioral nutrition research is supported through national research service awards, with training grants awarded to institutions and fellowships awarded to individuals.

Table 5. Actual Obligations, NIH Biomedical Nutrition Research and Training, by Category of Support, FY 1990 (in thousands of dollars)

		Breakdown		Total	
Funding Mechanism	Item	Number	Cost	Number	Cost
Extramural					
Research Grants	Regular	1,389	$149,394		
	Clinical Trials	109	27,249		
	Total			1,498	$176,643
Program Projects	Regular	79	25,472		
	Clinical Trials	5	2,380		
	Total			84	27,852
Contracts	Regular	141	22,899		
	Clinical Trials	13	3,174		
	Total			154	26,073
Centers	Regular	50	14,396		
	Clinical Trials	1	135		
	Total			51	14,531
Research Resources Support				294	22,564
Reimbursement Agreements				23	3,894
Career Development Awards				68*	2,812
Facilities Renovation/Repair				1	115
Training	Training Grants	45*	2,903		
	Fellowships	36*	609		
	Total			81*	3,512
Subtotal, Extramural					277,996
Intramural					
Projects				110	14,363
Training				3*	**
Subtotal, Intramural					14,363
Total NIH Biomedical Nutrition Research and Training					$292,359

*Number of training grants.
**Information not provided.

The intramural nutrition program consists of research projects and training.

The NIH FY 1990 actual obligations in biomedical nutrition research and training are shown by category of support in table 5. Of the $292 million expended by NIH on nutrition research and training in FY 1990, 95 percent supported extramural projects. The percentage of support for extramural projects is higher for NIH nutrition research funding than for total NIH research funding. Research grants comprised the largest category, with 1,498 projects supported at an expenditure of $177 million; of these, 109 projects, with an expenditure of $27 million, were clinical trials. Program projects formed the next largest category, with 84 projects (5 clinical trials) at a cost of $28 million ($2 million for clinical trials). Contracts comprised the third largest category, at 154 projects and $26 million, followed by research resources support at 294 projects and $23 million. The intramural program comprises $14 million or 5 percent of the total expenditures for nutrition research and training.

NUTRITION RESEARCH TRAINING

The NIH supports training in biomedical and behavioral nutrition research in both the extramural and the intramural programs. Within the extramural program, two basic mechanisms are used for nutrition training support: institutional awards and individual awards (see appendix J). The institutional awards, commonly called "training grants," are designed to enable institutions to make training awards to individuals selected by them for predoctoral and postdoctoral research training. In FY 1990, NIH spent $2.9 million on 45 training grants in nutrition. The predoctoral and postdoctoral individual national research service awards, called "fellowships," are awarded to provide pre- and postdoctoral research training to individuals to broaden their scientific background and extend their potential for research. In FY 1990, $609,000 was expended for 36 fellowships in nutrition.

Appendices

Legislative Base for Nutrition at the NIH

On November 20, 1985, the Health Research Extension Act of 1985 became Public Law 99-158. This act amended the Public Health Service Act "...to revise and extend the authorities under that Act relating to the National Institutes of Health and for other purposes."

Four institutes--the National Cancer Institute (NCI); National Heart, Lung, and Blood Institute (NHLBI); National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); and National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)--have specific mandates to conduct nutrition research at the NIH. These mandates are as follows:

NCI. Section 413(a)--"establish an information and education center to collect, identify, analyze, and disseminate on a timely basis, through publications and other appropriate means, to cancer patients and their families, physicians and other health professionals, and the general public, information on cancer research, diagnosis, prevention, and treatment (including information respecting nutrition programs for cancer patients and the relationship between nutrition and cancer)...."

NHLBI. Section 420--"(1)...dissemination of information regarding diet and nutrition, environmental pollutants, exercise, stress, hypertension, cigarette smoking, weight control, and other factors affecting the prevention of arteriosclerosis and other cardiovascular diseases and of pulmonary and blood diseases; and (2) the dissemination of information designed to encourage children to adopt healthful habits respecting the risk factors related to the prevention of such diseases...."

Section 421(a)(1)(A)--"investigation into the epidemiology, etiology, and prevention of all forms and aspects of heart, blood vessel, lung, and blood diseases, including investigations into the social, environmental, behavioral, nutritional, biological, and genetic determinants and influences involved in the epidemiology, etiology, and prevention of such diseases...."

NIDDK. Section 426--"conduct and support of research, training, health information dissemination, and other programs with respect to diabetes mellitus and endocrine and metabolic diseases, digestive diseases and nutritional disorders, and kidney, urologic, and hematologic diseases...."

Section 428--"(a)(1) In the Institute there shall be a Division Director for Diabetes, Endocrinology, and Metabolic Diseases, a Division Director for Digestive Diseases and Nutrition...responsible for--A) developing a coordinated plan (including recommendations for expenditures) for each of the national research institutes within the National Institutes of Health with respect to research and training concerning diabetes, endocrine and metabolic diseases, digestive diseases and nutrition, and kidney, urologic, and hematologic diseases; (B) assessing the adequacy of management approaches for the activities within such institutes concerning such diseases and nutrition and developing improved approaches if needed; (C) monitoring and reviewing expenditures by such institutes concerning such diseases and nutrition; and (D) identifying research opportunities concerning such diseases and nutrition and recommending ways to utilize such opportunities...(b)(1) carry out programs of support for research and training (other than training for which National Research Service Awards may be made under section 487) in the diagnosis, prevention, and treatment of diabetes mellitus and endocrine and metabolic diseases, digestive diseases and nutritional disorders, and...(2) establish programs of evaluation, planning, and dissemination of knowledge related to such research and training."

Section 432--"There are established within the advisory council for the Institute appointed under section 406 a subcommittee on diabetes and endocrine and metabolic diseases, a subcommittee on kidney, urologic, and hematologic diseases....The subcommittees are authorized to review applications made to the Director of the Institute for grants for research and training projects relating to the diagnosis, prevention, and treatment of the diseases for which the subcommittees are established and shall recommend to the advisory council those applications and contracts that the subcommittees determine will best carry out the purposes of the Institute. The subcommittees shall also review and evaluate the diabetes and endocrine and metabolic diseases, digestive diseases and nutrition, and kidney, urologic, and hematologic diseases programs of the Institute and recommend to the advisory council such changes in the administration of such programs as the subcommittees determine are necessary."

NIAMS. Section 440(6)--"...projects for investigation into the epidemiology of all forms and aspects of arthritis and musculoskeletal diseases, including investigations into the social, environmental, behavioral, nutritional, and genetic determinants and influences involved in the epidemiology of arthritis and musculoskeletal diseases...."

Other institutes that conduct and support nutrition research do so under much broader authority. Each conducts research programs in the "diagnosis, prevention, and treatment" of specific diseases and life processes within their areas of responsibility. These authorities are as follows:

- National Institute of Dental Research (NIDR): Section 453
- National Institute of Neurological Disorders and Stroke (NINDS): Section 457
- National Institute of Allergy and Infectious Diseases (NIAID): Section 446
- National Institute of General Medical Sciences (NIGMS): Section 461
- National Institute of Child Health and Human Development (NICHD): Section 448
- National Eye Institute (NEI): Section 445
- National Institute of Environmental Health Sciences (NIEHS): Section 463
- National Institute on Aging (NIA): Section 443
- National Center for Research Resources (NCRR): Section 479
- National Institute on Deafness and Other Communication Disorders (NIDCD): Section 464
- Fogarty International Center (FIC): International Cooperation Authority, Section 482
- National Center for Nursing Research (NCNR): Section 483
- Training Authority: Section 487

To facilitate and enhance the distribution of information regarding these specific disease areas to health professionals, patients, and the public, the following ICDs have established clearinghouses: NIDDK (Section 427) has established two clearinghouses, the National Digestive Diseases and Nutrition Clearinghouse and the National Kidney and Urologic Diseases Information Clearinghouse; NIAMS (Section 438 (b) has established the National Arthritis and Musculoskeletal and Skin Diseases Clearinghouse; the NIA (Section 4435E) Alzheimer's Disease Education and Referral (ADEAR) Center; and the NIDCD (Section 464B) National Deafness and Other Communication Disorders Information Clearinghouse. Nutrition information often is included.

In order to place more emphasis on research on health maintenance and disease prevention, the Health Research Extension Act of 1985 established the appointment of an Associate Director for Disease Prevention within the NIH Office of the Director (402(f)), NCI (416), and NICHD (451). A similar position exists at NHLBI (423) by current law. The associate directors are to "assure that each Institute's research plans include sections dealing with such prevention-related research as investigations into the epidemiology of disease; studies of the etiology of diseases (including the effect of diet and other personal habits on the development of disease, and the effect of environmental factors, including air, water, radiation, and toxic substances, on the development of disease); research into immunizations against disease; studies of the means to preclude the development of disease through changes in personal habits and environmental factors; and studies of methods for, and the cost-effectiveness of, population screening programs." In 1986, NIH established the Office of Disease Prevention (ODP) within the Office of the Director, under the purview of the NIH Associate Director for Disease Prevention. The Associate Director for Disease Prevention is responsible for promoting and coordinating the research programs of all Institutes regarding the prevention of disease.

Members of the NIH Nutrition Coordinating Committee[+]

Chairperson: Darla E. Danford, M.P.H., D.Sc., R.D.
DNRC

ICD*	Member/*Alternate*
NCI	Peter Greenwald, M.D. *Ritva Butrum, Ph.D.*
NHLBI	Nancy D. Ernst, M.S., R.D. *Karen Donato, M.S., R.D.*
NIDR	Joseph E. Ciardi, Ph.D.
NIDDK	Van S. Hubbard, M.D., Ph.D. *M. Kenneth May, Ph.D.*
NINDS	Vacant *Patricia H. Turner*
NIAID	Eugene M. Zimmerman, Ph.D.
NIGMS	Yvonne T. Maddox, Ph.D.
NICHD	Ephraim Y. Levin, M.D.
NEI	Barbara A. Underwood, Ph.D.
NIEHS	Thorsten Fjellstedt, Ph.D. *Michael J. Galvin, Jr., Ph.D.*
NIA	Ann W. Sorenson, Ph.D. *Judith G. Hallfrisch, Ph.D.*
NIAMS	Stephen P. Heyse, M.D. *Reva Lawrence, M.P.H.*
NIDCD	Jack Pearl, Ph.D. *Maureen Hannley, Ph.D.*
NCRR	Harriet Gordon, M.D. *Joseph J. Knapka, Ph.D.*
FIC	Kenneth Bridbord, M.D. *Ferdinand Hui, Ph.D.*
NCNR	John C. Chah, Ph.D.
NCHGR	Pamela Lokken

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*Institute, Center, Division

[+] As of September 1, 1990

NIH NCC Liaison Representatives

Organization	Member/*Alternate*
Clinical Center	Gloria Stables, M.S., R.D.
Division of Computer Research and Technology	Judith F. Mahaffey
Division of Legislative Analysis	Betsy Duane
Division of Research Grants	Ai Lien Wu, Ph.D. *Sooja Kim, Ph.D.*
National Library of Medicine	Harold A. Schoolman, M.D.
Office of Communications	Marc Stern
Nutrition Education Subcommittee	Karen Donato, M.S., R.D.

Interagency NCC Liaison Representatives

Organization	Member/*Alternate*
Alcohol, Drug Abuse, and Mental Health Administration	Susan Blumenthal, M.D., M.P.A. *Ellen Stover, Ph.D.*
Alcohol, Drug Abuse, and Mental Health Administration (Intramural)	Richard L. Veech, M.D. *Boris Tabakoff, Ph.D.*
Centers for Disease Control	Frederick Trowbridge, M.D. *Pamela M. Chin*
Food and Drug Administration	John Vanderveen, Ph.D. *Lynn A. Larsen, Ph.D.*
Health Resources and Services Administration	Elizabeth Brannon, M.S., R.D. *E. Ann Prendergast, R.D., M.P.H.*
National Center for Health Statistics	Clifford Johnson, M.S.P.H. *Carla Weinberg*
Office of Disease Prevention and Health Promotion, DHHS	Linda D. Meyers, Ph.D.
U.S. Department of Agriculture	Gerald F. Combs, Ph.D.

As of September 1, 1990

Members of the NCC Nutrition Education Subcommittee[+]

Chairperson and Executive Secretary: Karen Donato, M.S., R.D.
NHLBI

Organization	Member/*Alternate*
NHLBI	Nancy D. Ernst, M.S., R.D.
NCI	Ritva Butrum, Ph.D. *Luise Light, Ed.D.*
NIDDK	Van S. Hubbard, M.D., Ph.D.
NCRR	Bernard Talbot, M.D., Ph.D.
CC	Gloria Stables, M.S., R.D.
OC	Don Ralbovsky

[+] As of September 1, 1990

Members of the NCC Obesity Work Group[+]

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NCRR	Harriet Gordon, M.D.
NICHD	Gilman D. Grave, M.D. Ephraim Levin, M.D.
NCI	Ritva Butrum, Ph.D.
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NCNR	John C. Chah, Ph.D.
NINDS	Patricia Turner
NIAMS	Stephen P. Heyse, M.D.
NIEHS	Thorsten Fjellstedt, Ph.D.
NIDCD	Jack Pearl, Ph.D.
DNRC	Susan M. Pilch, Ph.D.

[+] As of September 1, 1990

NIH Task Force on the Nutrition Priority Area Year 2000 Health Objectives for the Nation[+]

Chairperson: Darla E. Danford, M.P.H., D.Sc., R.D.
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ICD*	Member
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NIA	Ann W. Sorenson, Ph.D.
NIAMS	Stephen P. Heyse, M.D.
Nutrition Education Subcommittee Liaison	Karen Donato, M.S., R.D.

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*Institute, Center, Division

[+] As of September 1, 1990

Program Announcements, Requests for Applications, and Requests for Proposals in Nutrition, FY 1990

A major responsibility of the DNRC and its NCC is to identify areas for further research and bring them to the attention of the institutes for the development and publication of program announcements (PAs), requests for applications (RFAs), and requests for proposals (RFPs). When areas of nutrition research are of interest to more than one institute, including those of Alcohol, Drug Abuse, and Mental Health Administration, joint PAs often are developed under the auspices of the NCC.

- A PA is a formal statement of an NIH extramural research activity or of the initiation of a new or modified mechanism of support. It may describe new or modified program interests or simply be a reminder of continuing interest.

- An RFA is a formal statement that invites grant applications in a well-defined scientific area to accomplish specific program purposes, generally identifies only one application receipt date, and indicates whether or not funds have been set aside for the competition and, if so, the amount of funds and/or the expected number of awards to be made. An RFA may be reissued as necessary.

- An RFP is the government's invitation to prospective offerors to submit a contract proposal based on the terms and conditions set forth in the RFP by the statement of work that describes the nature of intended procurement. The number of contracts awarded as a result of an RFP is smaller than the number of applications funded as a result of PAs and RFAs.

PAs, RFAs, and RFPs in nutrition research and training published in the *NIH Guide for Grants and Contracts* in FY 1990 follow in chronological order.

Issued by	*Date*	*Type*	*Title*
NIDDK	10/89	RFA	Digestive Diseases Core Centers
NIDR	10/89	RFA	Clinical Dental Research Core Centers
NCI	10/89	RFP	Large Bowel Adenomatous Polyp Dietary Intervention Study–Clinical Centers
NIDR	10/89	PA	Nutrition Research and Oral Health
NICHD	11/89	RFP	Trial of Calcium Supplementation in Pregnancy for the Prevention of Preeclampsia and Preterm Birth
NICHD	11/89	RFP	The Data Coordinating Center for the NICHD Trial of Calcium Supplementation in Pregnancy for the Prevention of Preeclampsia and Preterm Birth
NCI	12/89	RFA	Prevention Clinical Trials Utilizing Intermediate Endpoints and their Modulation by Chemopreventive Agents
NIDDK NIA	12/89	RFA	Core Grants for Clinical Nutrition Research Units
NCNR NICHD	12/89	PA	Neonatal Nursing Care of Low Birthweight Infants

NIDDK	12/89	RFA	Obesity Research Center (Core Center) Grant
NIDCD	12/89	PA	Taste System Plasticity: Development, Maintenance, and Regeneration
NICHD	1/90	RFA	Child Health Research Centers
NCI	1/90	RFA	Synthesis of Compounds for Boron Neutron Capture Therapy
NICHD	1/90	RFA	Cooperative Multicenter Network of Maternal-Fetal Medicine Units
NICHD	1/90	RFA	Cooperative Multicenter Network of Neonatal Intensive Care Units
NIDDK	1/90	RFA	Kidney Disease of Diabetes Mellitus: Pathophysiology, Clinical Features, and Epidemiology
NIDCD	2/90	PA	Central Taste Pathways and Neurochemistry
NICHD NIDDK	2/90	RFA	Genetic and Metabolic Factors in Obesity
NIDDK NICHD	2/90	RFA	Research Training and Career Development Awards in Nutrition
NICHD	3/90	RFA	Cooperative Multicenter Network of Neonatal Intensive Care Units
NICHD	3/90	RFA	Functional Tests of Nutritional Status in Pregnant Women, Infants, and Children
NHLBI	3/90	RFA	Cost-Effective Strategies of Cholesterol-Lowering
NIDDK	3/90	RFA	Addendum: Kidney Diseases of Diabetes Mellitus: Pathophysiology, Clinical Features, and Epidemiology
NICHD	3/90	RFA	Request for Research Center Core Grant Applications: Mental Retardation Research Centers
NIDDK	4/90	PA	The Study of the Etiology and Pathogenesis of Inflammatory Bowel Disease
NIDDK	5/90	RFA	Diabetes Centers
NCI	5/90	PA	Obesity, Endocrine and Fat Metabolism and Cancer Risk
NICHD	6/90	RFA	Perinatal Emphasis Research Centers
NHLBI	7/90	RFA	CVD Nutrition Education for Low Literacy Skills
NHLBI	8/90	RFA	Comprehensive Sickle Cell Center Program

NIH Guide Notices

NIH ADAMHA	2/90	Notice	Inventions: Important Notice for Research Grantees and Research Contractors
NIH ADAMHA	3/90	Notice	Implementation of New Restrictions on Lobbying Regarding Grants and Cooperative Agreements
NIH ADAMHA	3/90	Notice	Health and Safety Guidelines for Grantees and Contractors
NIH	3/90	Notice	Availability of Fish Oil Test Materials
NIH ADAMHA	8/90	Notice	NIH/ADAMHA Policy Concerning Inclusion of Women in Study Populations
PHS	9/90	Notice	Final Rules - Grantee Requirements for Drug-free Workplace
ADAMHA NIH	9/90	Notice	ADAMHA/NIH Policy Concerning Inclusion of Minorities in Study Populations

Appendix D

Nutrition-sponsored Conferences and Workshops, FY 1990

NHLBI	Workshop on Salt and Blood Pressure November 1-2, 1989
FIC	9th Annual Calcium Day Conference: Intracellular Handling of Calcium January 12, 1990
NIDDK	Workshop on Regulation of Energy Expenditure January 28, 1990
NIAMS, NIDDK NIA	Conference on Research Advances in Osteoporosis February 26-28, 1990
NIA	International Conference on Biological Effects of Dietary Restriction March 5-7, 1990
NHLBI, NIA	Workshop on Heart-healthy Diets for Older Americans: Issues and Opportunities March 7-8, 1990
NCI, NICHD	FASEB Summer Research Conference on Retinoids June 17-22, 1990
NHLBI	Gordon Research Conference on Lipid Metabolism June 18-22, 1990
NIGMS, NCC	Research Conference on Advances in Understanding Trauma and Burn Injury June 21-23, 1990
NHLBI	FASEB Summer Research Conference on the Synthesis and Function of Vitamin K-dependent Proteins July 22-27, 1990
NIDDK	FASEB Summer Research Conference on Folic Acid, Vitamin B-12, and One-carbon Metabolism July 29-August 3, 1990
NCC, DNRC	Planning Meeting on the Biomedical Aspects of Obesity: Prevention and Treatment August 3, 1990
NIDDK	FASEB Summer Research Conference on Intestinal Lipid Absorption, Metabolism, and Transport August 12-17, 1990
ICHNR, DNRC	Human Nutrition Research Information Management System Meeting August 13-14, 1990
NHLBI	Workshop on Obesity and Cardiovascular Disease in Minority Populations August 28-29, 1990

NIDDK, NCI	Symposium on Ascorbic Acid: Biological Functions and Relation to Cancer September 10-12, 1990
NHLBI	Workshop on Costs and Health Implications of Cholesterol Lowering September 17-18, 1990

Abstracts from NCC-sponsored Scientific Seminars, FY 1990

New Fruit, Vegetable, and Selected Phytochemical Research Program in Cancer Prevention

Herbert F. Pierson, Ph.D., Toxicologist, Diet and Cancer Branch, NCI, NIH, Rockville, MD (October 1, 1989)

Hundreds of safe non-nutritive phytochemicals are found in edible plants. The phytochemicals in edible fruits and vegetables can be grouped into two general categories for relevance to cancer prevention studies applied to humans. The first category is comprised of those substances that are present in limited quantities, exhibit chemical uniqueness in their structures, and are found only in specific fruits and vegetables. By virtue of their uniqueness these substances could rationally be incorporated into experimental foods as compliance markers. Substances in this category might include rare tocopherols, isomeric isoprenoids, unusual methoxylated flavanoids, and uncommon heterocyclic and hydrocarbon-based plant pigments. The second category of phytochemicals are those that are found in higher quantities, occur in several edible species, and may be ingested by humans daily in gram quantities. This second group exhibits a potential for modulating human metabolism in a manner favorable for cancer prevention. Examples of these phytochemicals include classes of indoles, sulfides, terpenes, isothiocyanates, phenolic glycosides, bioflavanoids, coumarins and other lactones, lignans, carotenoids, sterols, naphthoquinones, saponins, tetrapyrroles, and polyacetylanes. Both of the above two general categories of fruit and vegetable phytochemicals merit intense study, but with different orientations. It is the major objective of this program to develop analytical methodology for detecting and quantifying phytochemicals in experimental food fortifications, in the blood and urine of humans consuming these experimental foods, and for assessing metabolic changes pertinent to cancer prevention in humans.

Cellular Uptake of Retinol

Kaare R. Norum, M.D., Ph.D., Fogarty Scholar at the NIH, Professor of Medicine, Institute for Nutrition Research, School of Medicine, University of Oslo, Norway (February 5, 1990)

Retinoids may have roles in prevention and probably therapy of cancer and premalignancies. The recent discoveries of retinoic acid as a morphogen, the retinoic acid receptors, and retinoic acid receptor responsive elements on several genes have led to a great increase in the interest of vitamin A. Retinol enters the enterocytes in the gut via facilitated diffusion. In the enterocytes the retinol is esterified with long chain fatty acids, due to either lecithin:retinol acyltransferase (LRAT) or acyl:CoA retinol acyltransferase (ARAT) or both.

Retinyl esters leave the gut via chylomicrons and stay with the chylomicrons remnants, which is taken up mostly by the liver, but also by bone marrow and spleen in some animal species.

Uptake in the liver is via receptor-mediated endocytosis by the hepatic parenchymal cells. Newly absorbed retinyl esters are hydrolyzed and transferred to the perisinusoidal stellate cells for storage. More than 90 percent of the liver storage of vitamin A is as retinyl esters in the stellate cells. These cells have the capacity to secrete retinol bound to plasma retinol binding protein (RBP). Both parenchymal cells and stellate cells can take up retinol from RBP, and both cell types seem to have receptors for RBP.

Chylomicron remnants (labeled with retinyl esters) are taken up by the bone marrow of rabbits and primates. The cells responsible for the uptake are macrophages. Retinol may also be taken up by peripheral white blood cells , and by leukemic cell of the myeliod type. The uptake may go via the retinol-RBP complex or via lipoproteins (both chylomicrons and low density lipoproteins). After a meal with high amounts of retinol, the concentration of retinylesters in chylomicrons is high enough to induce differentiation and stop proliferation of immature leukemic cells. Thus, retinol may therefore be an adjuvance in the treatment of acute myelogenous leukemia. Such trials are in progress in Scandinavia.

Obesity and Associated Risk Factors

Barbara C. Hansen, Ph.D., Professor of Physiology, School of Medicine, University of Maryland, Baltimore, MD (March 1, 1990)

An estimated 34 million Americans are "overweight" and of those, 11 million are considered "seriously obese." Further, weight loss attempts cost Americans upwards of $30 billion dollars per year. Nevertheless, with all of these weight loss attempts, two thirds of those who do lose weight, regain more! Only 2 to 4 percent of those who lose weight seem to be able to keep it off. Obesity is well known to be associated with an increased incidence of heart disease, hypertension, certain cancers, and type II noninsulin-dependent diabetes mellitus. Clearly, obesity constitutes a major health and treatment problem. Only by greater understanding of the mechanisms underlying obesity and its associated complications and risk factors are we likely to be successful in mitigating this disturbance in energy balance.

We have developed a nonhuman primate model of spontaneous obesity and diabetes which shows remarkable similarities to the human conditions. Its special features include that the time course for the development of these disorders is compressed so that obesity becomes apparent between 8 and 12 years of age, and overt diabetes can be identified in some but not all obese in the age range 10 to 20 years, middle age for a rhesus monkey. Because these animals are being kept under ideal, well-protected, carefully cared for conditions, with *ad libitum* food intake, we have recently been able to describe in detail the prodrome of physiological and cellular disturbances which precede overt diabetes. Studies are underway to attempt to alter this progressive process, and to slow or to stop the development of diabetes with its many complications and high morbidity and increased mortality.

As in humans, these rhesus monkeys have so far been shown to develop obesity without significant increase in caloric intake, and some of those who are obese develop an increasing degree of insulin resistance and hyperinsulinemia. Eventually, the most resistant show a deterioration in pancreatic function, an increase in hepatic glucose production, and gradually progressive hyperglycemia. Finally, this model appears to develop most, and possibly all of the complications associated with longstanding diabetes in man--nephropathy, retinopathy, peripheral neuropathy, and cardiovascular disease.

Malignant Obesity: Definition, Pathophysiology and Treatment

John G. Kral, M.D., Ph.D., Professor of Surgery, SUNY Downstate Medical Center, Brooklyn, NY (March 2, 1990)

Definition

Even though knowledge that obesity truly is a disease might seem widespread, acceptance of the fact by large sectors of the lay public and health professionals is limited. Prevailing attitudes view obesity at best as a cosmetic disturbance, at worst as an immoral self-inflicted condition unworthy of treatment.

The term "morbid obesity" was coined in the early 1960s to focus attention on a degree of obesity associated with manifest other morbidity. Obviously the term is both redundant grammatically and conceptually flawed, perpetuating the premise that there exists obesity that is not a disease.

The frequent use of the term "co-morbidity" for conditions potentially caused by obesity has similar implications. Obesity is denied a role as primary risk factor for these conditions and is not mentioned as a leading cause of death in U.S. mortality statistics. However, in 1986 the seven leading causes of death in the U.S., accounting for 80 percent of all mortality, are incontrovertibly associated with obesity. Treatment of obesity, it seems, can only be legitimized in the face of "acceptable" diseases such as diabetes, heart failure, pulmonary compromise, osteoarthritis, etc.

Ample epidemiologic evidence has demonstrated the importance of fat distribution for morbidity and mortality. Abdominal (central, truncal or "android") habitus is associated with obesity-related morbidity in contrast to gluteal (peripheral, femoral or "gynoid") distribution of fat. Thus it seems that there might be some merit to differentiating between forms of obesity based on their prognosis.

It is proposed that the term "malignant obesity" be used to describe the progressive, intractable, lethal form of obesity, recognizing its association with various cancers and its cell-proliferative, hyperplastic nature. Criteria for malignant obesity are outlined in the table. Obesity, associated with any of the following can be considered "malignant" requiring serious treatment:

History of an event:
- myocardial infarction
- stroke
- pulmonary embolus

Existence of risk factor(s):
- abdominal fat distribution
- diabetes or glucose intolerance
- smoking
- dyslipoproteinemia
- hypertension

Other manifest morbidity:
- heart failure
- respiratory insufficiency
- obesity-related cancer
- sleep apnea

Family history of any of the above.

Pathophysiological studies

The majority of studies of fat distribution are epidemiologic, showing associations between increasing waist:hip ratio and manifest disease. Our studies of severely obese candidates for surgical treatment of obesity have revealed numerous physiological correlates of abdominal distribution of adipose tissue. Using cardiac radionuclide imaging we demonstrated ventricular dysfunction with increasing waist:hip ratio in asymptomatic obese women. Similarly pulmonary diffusion capacity, an adaptive phenomenon, was increased with increasing abdominal distribution of fat. These cardiac and pulmonary findings were associated with increasing proportion of extracellular water, likely reflecting incipient edema. Liver biopsies at the time of anti-obesity surgery revealed increased fatty infiltration with increasing waist:hip ratio without any correlation with body weight or body fat in patients of both sexes. We speculate that the increased steatosis is of pathogenetic importance for the development of hypertriglyceridemia and atherosclerosis and is mediated via increased meal-stimulated insulin release. Others have demonstrated increased meal-stimulated insulin and gastrointestinal polypeptide release in obese patients compared to normal controls. Our laboratory studies of eating rate in the presurgical patients revealed a correlation between eating rate and waist:hip ratio: the more abdominal distribution of fat, the faster the eating rate. Hypothetically, eating behavior would seem to have an important primary role in the pathogenesis of the metabolic aberrations of obesity, in turn leading to significant morbidity.

Treatment

The greater the body weight, the poorer are the results of treatment. In fact there are no published data of patients who have managed to maintain significant weight loss beyond 1 year of followup with diet, exercise, medication, behavior modification or any nonsurgical modality.

Two basic principles are employed management of obesity: gastric restriction (as in gastroplasty) and malabsorption (as in intestinal bypass). Gastric bypass uses both principles, though it seems the malabsorptive or maldigestive component by causing dumping has an aversive effect that potentiates the gastric restriction.

Immediate effects of any surgical procedure for obesity are normalization of glycemia and hypertension even prior to weight reduction. Gradual improvement of respiration, hyperlipidemia, and heart failure occur during the first 3 months following surgery and seem to be sustained, even with a moderate regain of weight between 2-5 years postoperative. The revision rate and long term failure of weight loss maintenance are of great concern to surgeons in this field. Reoperations are less safe and it is unclear whether long-term results of reoperation are acceptable. Improved patient selection might improve results. Several recent studies comparing gastroplasty with gastric bypass have unequivocally demonstrated superior weight loss and long term maintenance with gastric bypass. In attempts to improve results of gastric bypass, attempts have been made to lengthen the bypassed segments of small intestine. It has yet to be determined whether there are optimal proportions of small bowel in continuity with varying stomach size or whether staged surgery is safer and more efficacious over the long term. Increasing prevalence of obesity in the U.S. and identification of markers for malignant obesity indicate the need for rigorous study of surgical treatment of obesity.

Racial/Ethnic Difference In Obesity and Associated Cardiovascular (CVD) Morbidity and Mortality

Shiriki Kumanyika, Ph.D., Associate Professor of Nutritional Epidemiology and Epidemiology, Pennsylvania State University, University Park, PA (March 21, 1990)

The subpopulations classified as U.S. minorities are extremely diverse, not only in terms of racial/ethnic and cultural heritage but also in regard to demographic factors such as the proportion who are recent immigrants, who live in various geographic regions or in urban vs. rural areas, and who are poor (although all minority groups have a disproportionate percentage of persons living in poverty in comparison to whites). Moreover, the four major minority group classifications used for census purposes--black, Hispanic, Asian/Pacific Islander, and Native American--are far from homogeneous. The extent of heterogeneity is largest for the numerically smallest groups. In the 1980 census, Native Americans and 97 percent of black Americans were U.S. born, whereas 29 percent of Hispanic Americans and 68 percent of Asian/Pacific Islanders were immigrants.

Obesity is much more prevalent in almost all minority group men and women than in white (non-Hispanic) men and women (some Asian American populations are exceptions). Although racial/ethnic differences in body proportion may influence prevalence estimates, the observed differences are too large to be artifactual, and only some of the differences are explained by the association of female obesity with low socioeconomic status. The nature of the common characteristic of these different minority subgroups that predisposes to obesity is unclear. Genetic factors have not been ruled out; but plausible environmental explanations can be advanced and may be sufficient.

Interestingly, current patterns of CVD morbidity and mortality across minority populations reflect a range of susceptibility to the health impacts of obesity. Diabetes mellitus, which is strongly associated with obesity and is a risk factor for CVD, occurs disproportionately in all minority groups in comparison to whites, even in the Asian American subgroups who are not, on average, more obese than whites. In contrast, mortality from other obesity-related conditions such as hypertension and heart disease is higher than average in black Americans and lower than average in most or all of the other minority subgroups. These lower than average rates of certain CVD manifestations in the presence of higher than average rates of obesity and diabetes may offer a unique opportunity for prevention. That is, considering that degenerative diseases increase in populations as infectious diseases recede in importance, future CVD morbidity and mortality patterns in other minority groups may approach those currently observed in blacks. Thus, the conclusion that Hispanic, Asian/Pacific Islanders, or American Indians are somehow "protected" from the harmful effects of obesity would seem premature, especially while the evidence is still so limited and until a secular trend to the contrary can be ruled out.

Measurement of Total Body Fatness

Alex F. Roche, M.D., Ph.D., D.Sc., Professor, Department of Community Health, Wright State University School of Medicine (March 21, 1990)

Some current methods were reviewed with an emphasis on densitometry and comments about the advantages and limitations of total body electrical conductivity and neutron activation. Finally, attention was directed to the need to apply predictive equations in the context of epidemiological studies.

Densitometry is applicable during a limited age range, and it is not appropriate for people with some diseases. The simplistic view that the body is composed of fat and fat-free mass must be replaced by a multicomponent model in which the body is considered to consist of fat, water, mineral, and protein. Age- and sex-specific data are available for the expected proportions of these components of fat-free mass at ages up to 25 years; corresponding data are lacking for older ages. After 25 years, and preferably before it also, densitometry should be performed in combination with measurements of total body bone mineral and total body water so that the proportions of these in the body can be calculated for individuals and the multicomponent model can be applied. Total body bone mineral is best obtained from dual energy x-ray, and total body water can be obtained from the dilution of deuterium oxide. Proper implementation of these procedures should result in accurate values for body composition, calculated from body density.

Alternatives include total body electrical conductivity (TOBEC), which is noninvasive and subject to the same influences of variations in the composition of FFM that have been noted for densitometry. A final alternative to be considered is neutron activation which is available in very few sites and cannot be recommended because of the high cost in dollars and radiation.

The most accurate methods for measuring body composition *in vitro* are appropriate for the study of small groups but not for surveys. Surveys require the application of predictive equations developed from sets of data that include accurate measures of the dependent and independent variables. The dependent variable should be obtained in the manner outlined above. The independent variables tested for inclusion should be those likely to be associated with the dependent variable. It is recommended that the dependent variable be fat-free mass and that the independent variables include bioelectric resistance and reactance, in addition to anthropometric variables that are closely related to the size and shape of the fat-free mass. Of course, an estimate of fat-free mass can easily lead to estimates of body fatness if weight is measured. Modern statistical procedures should be used to develop predictive equations. The application of all possible subsets regression, together with ridge and robust procedures, is likely to produce good results that will be replicated in on cross-validation. Such equations should be considered for use in surveys.

Nutrition Education Subcommittee Procedures

All nutrition publications and materials prepared for the public by any of the components of the NIH are to be brought to the attention of the NIH Nutrition Education Subcommittee for review and comment. Adherence by the institutes to the subcommittee's recommendations is required, and all revisions of publications/materials are to be brought to the attention of the Nutrition Education Subcommittee chairperson before their final publication.

PROCESS

The ICD information officers and/or NCC members are to bring to the attention of the Nutrition Education Subcommittee chairperson all nutrition publications/materials destined for the public when they are close to the final draft stages, prior to their review for institute clearance review.

- The Nutrition Education Subcommittee is asked to review and comment on the draft and provide comments to the chairperson within 2 weeks. The comments are then collated and discussed at a meeting of the subcommittee in the presence of the appropriate initiating institute staff. The final comments evolving from the subcommittee meeting are then transmitted to institute staff and NCC members for action.
- Problems with incorporating the subcommittee's comments are to be discussed and resolved with the subcommittee chairperson and respective ICD-NCC representative. If such problems are not resolved, the entire NCC will be asked to provide comment. The revised version of the publication is to be brought to the attention of the chairperson to assure accuracy and consistency. Depending on the extent of the revision, a second review by the entire subcommittee may be required.
- After the publication has been cleared by the institute, the final revised version is to be brought to the attention of the Nutrition Education Subcommittee chairperson.
- Sample copies of all printed publications and information regarding availability should be provided to the Nutrition Education Subcommittee chairperson and the NCC office in order to keep up-to-date the list of nutrition publications available to the public from the various NIH institutes.

CONTENT

Each publication is reviewed for the following:

- Scientific accuracy. All information is based on the best current scientific evidence. Areas known to be controversial also need to be addressed to avoid misinterpretation by the public.
- Consistency with other NIH nutrition publications to avoid mixed messages.
- Compatibility with the *Dietary Guidelines for Americans*. Because the guidelines serve as the basis for all Federal dietary guidance to the general public, publications directed toward most healthy Americans must support the tenets of the dietary guidelines.
- Identification of the intended audience (e.g., adults, children, etc.) and the ability to meet the specific needs of the intended target group, be it the healthy general public or other subpopulation groups (e.g., patient populations, minority groups, etc.). For example, the reading level needs to conform to the needs of the target audience, and publications should be culturally relevant.
- Avoidance of mention of specific brand names of foods or other items that can be misconstrued as NIH endorsement.
- Appeal and clarity of the overall publication, title, graphs, illustrations, and charts to illustrate difficult concepts.

NIH Nutrition Publications Reviewed by the Nutrition Education Subcommittee

The publications listed below are available from the offices listed; all addresses are National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892.

Institute/Publication	Pub. No.
National Cancer Institute Office of Cancer Communications Building 31, Room 10A18	
Good News, Better News, Best News...Cancer Prevention	84-2671
Diet, Nutrition, and Cancer Prevention...A Guide to Food Choices	87-2878
Diet, Nutrition and Cancer Prevention...The Good News	87-2878
Eating for Life	88-3000
Eating Hints - Tips and Recipes for Better Nutrition During Cancer Treatment (intended for patients)	91-2079
National Heart, Lung, and Blood Institute Information Office Building 31, Room 4A21	
Questions About Weight, Salt and High Blood Pressure	84-1459
Facts About Blood Cholesterol (revised)	90-2696
Healthy Heart Handbook for Women	87-2720
Eating for Life	88-3000
Check Your Weight and Heart Disease I.Q.	90-3034
NHLBI Kit '90: The Right Moves	NN-315
National Institute on Aging Information Office Federal Building, Room 6C12	
Be Sensible About Salt	Age Page
Osteoporosis: The Bone Thinner	Age Page
Dietary Supplements: More Is Not Always Better	Age Page
Nutrition: A Lifelong Concern	Age Page
Hints for Shopping, Cooking, and Enjoying Meals	Age Page

Institute/Publication	Pub. No.
National Institute of Dental Research **Office of Communications** **Building 31, Room 2C35**	
A Healthy Mouth for You and Your Baby	86-1255
Fluoride to Protect the Teeth of Adults	87-2329
National Institute of Diabetes and Digestive and Kidney Diseases **Information Office** **Building 31, Room 9A04**	
Irritable Bowel Syndrome	87-693
Noninsulin-Dependent Diabetes (intended for patients)	87-241
National Institute of Arthritis and Musculoskeletal and Skin Diseases **Information Office** **Building 31, Room 4C05**	
Osteoporosis - Cause, Treatment, Prevention (*Send a SASE for a single copy; for multiple copies, contact the office above for price list)	86-2226*
National Institute of Child Health and Human Development **Information Office** **Building 31, Room 2A32**	
Understanding Gestational Diabetes—A Practical Guide to a Healthy Pregnancy	89-2788
Division of Nutrition Research Coordination **Building 31, Room 4B63**	
Nutrition Research at the NIH	90-2611

Appendix H

Availability of Fish Oil Test Materials

FISH OIL TEST MATERIALS PROGRAM

The Fish Oil Test Materials Program is administered by the DNRC, NIH. The program was established in 1986 through the cooperation of the NIH, ADAMHA, and NOAA/DOC. This program has been designed to provide a long-term, consistent supply of quality-assured/quality-controlled test materials to researchers in order to facilitate the evaluation of the role that omega-3 fatty acids play in health and disease. The test materials are produced and supplied by NOAA/DOC at the National Marine Fisheries Service Southeast Fisheries Science Center Charleston Laboratory in Charleston, South Carolina.

Fish Oil Test Materials Advisory Committee

A Fish Oil Test Materials Advisory Committee (FOTMAC) is cochaired by scientific staff from NIH and ADAMHA and is composed of scientists representing the funding agencies (NIH, ADAMHA), the research community, DOC, and the FDA. The FOTMAC is advisory to the DOC regarding the types of materials needed by research scientists, shipping procedures for the materials, additional quality control and production issues, and general programmatic issues, such as future directions. The FOTMAC has produced a manual on "Good Laboratory Practices" for the handling of polyunsaturated materials. In addition, the committee provided guidance to DOC during the production of the Drug Master File submitted to the FDA by the FOTMAC. Manuals on "Analytical Methods for the Quality Assurance of Fish Oil, Production Methods/Safety and Distribution" were produced by the DOC.

Fish Oil Test Materials Distribution Committee

A Fish Oil Test Materials Distribution Committee (FOTMDC) is composed of NIH and other Federal scientists who do not use these products. The FOTMDC processes the applications received from investigators on a quarterly basis, advises the DOC of applicants who have fulfilled the application process, and makes recommendations to DOC regarding the distribution of requested materials.

TEST MATERIALS CURRENTLY AVAILABLE

- EPA Ethyl Ester

The ethyl ester of EPA is prepared from vacuum-deodorized menhaden oil using transesterfication, urea adduction and short-path distillation to yield an n-3 ethyl ester concentrate. The purified ethyl ester of EPA is attained by supercritical fluid CO_2 extraction from the n-3 ethyl ester concentrate followed by high performance liquid chromatography. The product contains >95% ethyl esters; of the ethyl esters EPA is 97%, other n-3's are <1%, n-6's are <1% and other fatty acids are <1%.

- DHA Ethyl Ester

The ethyl ester of DHA is prepared from vacuum-deodorized menhaden oil using transesterfication, urea adduction and short-path distillation to yield an n-3 ethyl ester concentrate. The purified ethyl ester of DHA is attained by supercritical fluid CO_2 extraction from the n-3 ethyl ester concentrate followed by high performance liquid chromatography. The product contains >95% ethyl esters; of the ethyl esters DHA is 96%, other n-3's are <2%, n-6's are <1% and other fatty acids are <1%.

- n-3 Ethyl Ester Concentrate

The n-3 ethyl ester concentrate is prepared from vacuum deodorized menhaden oil using transesterification, urea adduction and short-path distillation. The concentrate contains approximately 80% n-3 fatty acid ethyl esters (44% EPA, 24% DHA, 10-12% other n-3 fatty acid ethyl esters), 3% C18 (other than n-3), 6% C16 and the remainder as other esters. It contains 0.2 mg/g TBHQ as antioxidant, 2 mg/g tocopherols and 2.0 mg/g cholesterol. The concentrate is available in 1 g soft-gel capsules (100 capsules/bottle) or packaged in bulk in quantities suitable to investigators needs.

- Placebo Ethyl Esters

The ethyl esters of virgin olive oil are prepared by transesterification. The preparation contains approximately 70% oleic acid, 13% C16, and 15% C18 (<1% n-3) fatty acid ethyl esters. It contains 0.2 mg/g TBHQ as antioxidant and 2 mg/g tocopherols. The preparation is available in 1 g soft-gel capsules (100 capsules/ bottle) or packaged in bulk in quantities suitable to investigators needs.

- Deodorized Menhaden Oil

Deodorized menhaden oil is prepared from oil that has been winterized and alkali refined; it is processed through a two-stage wiped-film evaporator to remove cholesterol, volatile oxidation products, and any traces of organic contaminants. The oil contains approximately 30% n-3 fatty acids in the triglyceride form, 14% EPA, 8% DHA, and 8% other n-3. It contains 0.2 mg/g TBHQ as antioxidant, 2 mg/g tocopherols and 2.0 mg/g cholesterol. The deodorized oil is available in 1 g soft-gel capsules (100 capsules/bottle) or is packaged in bulk quantities suitable to investigators needs. Special requests for antioxidant free oil may be entertained.

- Placebo Oils

Commercial preparations of corn, olive, and safflower oil have been soft-gel encapsulated to serve as placebos for the encapsulated menhaden oil. These oils contain 0.2 mg/g TBHQ as antioxidant and 2 mg/g tocopherols. The major fatty acids for each oil are corn (58% 18:2n-6, 26% 18:1n-9), olive (17% 18:2n-6, 57% 18:1n-9), and safflower (80% 18:2n-6, 9% 18:1n-9). They are available in 1 g soft-gel capsules (100 capsules/bottle). Investigators may request analysis of antioxidant and tocopherol levels in oil purchased for use as placebos for bulk menhaden oil.

APPLICATION PROCESS

To qualify to receive materials described in this announcement the applicant must 1) have a peer-reviewed research project indicating the need for the requested materials, and 2) submit a correctly completed application form and a signed waiver of liability. The committee will not be responsible for assessing the scientific merit of the application. Regulations on human subjects and animal research apply. In accordance with federal regulations, an IND number will be required for the use of these materials in human studies. The FOTMAC has established a drug master file at the FDA which includes manufacturing, chemical composition, and toxicological data relevant to these products. Investigators using NOAA/DOC materials may reference this file in order to expedite their IND requests. Availability of materials are contingent on DOC/ NOAA production capabilities. When prioritization is necessary, the order will be 1) NIH/ADAMHA funded, 2) other U.S. government funded, 3) peer-reviewed, other funded, 4) NIH/ADAMHA approved, not funded, and 5) other.

TEST MATERIALS AVAILABLE IN THE FUTURE

Test materials and their relevant application process will be announced in the *NIH Guide for Grants and Contracts* as new materials become available.

OTHER INFORMATION

Additional information will be provided to the investigator in the form of complete quality assurance data for each lot of test material shipped, stability data, and storage instructions.

INQUIRIES AND APPLICATIONS

Investigators may obtain further information and apply for available fish oil test materials for relevant studies by requesting an application form from:

Fish Oil Test Materials Program Coordinator
Division of Nutrition Research Coordination
Building 31, Room 4B63
National Institutes of Health
Bethesda, Maryland 20892
301-496-2323

Appendix I

HNRIM System Classification Codes

The development of the Human Nutrition Research Information Management (HNRIM) System, which was established in 1982, began with the work of the NCC. Since 1977, the NCC has retrieved data on NIH projects with nutrition research and training components and their nutrition expenditures, based on the definition of human nutrition research developed by the NCC. The HNRIM System is managed by the DNRC, under the auspices of the ICHNR.

The Joint Subcommittee on Human Nutrition Research, operating out of the Office of Science and Technology Policy in the Executive Office of the President, expanded the NIH definition and data collection system to include the human nutrition research activities supported by participating Federal agencies, and developed a system of 34 data classification categories for human nutrition research. In FY 1985, Code 35, "Parenteral, Enteral, and Elemental Nutrition," was added, and the NIH Special Interest Areas were assigned to codes 51-56. The FY 1990 NIH nutrition research program is presented in accordance with this classification system, which is used by the HNRIM System.

The nutrition projects in the system are classified under five major areas, and research in the biomedical and behavioral sciences is subclassified under three major components. The system is subsequently divided into 35 categories. Each nutrition research project is assigned classifications, and as many classifications as are needed are chosen in order to adequately identify all major nutrition aspects of the research project. Additional codes are assigned to special interest areas of the NIH.

I. Research in the Biomedical and Behavioral Sciences

A. Research on Normal Nutritional Requirements Throughout the Life Cycle

The following five categories are included because of the importance to health promotion of establishing normal nutritional requirements throughout the life cycle, and the differing needs of individuals at various stages of the life cycle.

Research activities relevant to normal nutrition at specific stages of the human life cycle should be assigned to classifications 1-5.

1. **Maternal Nutrition**

2. **Infant and Child Nutrition** (0-12 years)
(Includes the low birth weight infant)

3. **Adolescent Nutrition** (13-18 years)

4. **Adult Nutrition** (19-65 years)

5. **Nutrition of the Elderly** (65+ years)

B. Diseases and Conditions

Research on the role of nutrition in the prevention, amelioration, and treatment of diseases and conditions should be assigned to categories 6-16.

Because of the importance of appropriate nutritional support of the patient in the treatment of disease, the category of "parenteral, enteral, and elemental nutrition" has been added in this subsection as code 35.

6. Cardiovascular Disease and Nutrition

7. Cancer and Nutrition

8. Other Diseases and Nutrition
(e.g., osteoporosis, diabetes, etc.)

9. Trauma (Including Burns) and Nutrition

10. Infection--Immunology and Nutrition

11. Obesity, Anorexia, and Appetite Control

12. Genetics and Nutrition

13. Nutrition and Function
(Includes mental, psychomotor, and work performance; environmental stress)

***14. Nutrient Interactions**
(Includes nutrient-nutrient interactions, nutrient-drug interactions, nutrient-toxicant interactions, and nutrient toxicity)

15. Other Conditions and Nutrition

***16. Nutritional Status**
(Includes research on methods for the determination of nutritional status and surveillance: dietary history and food consumption, biochemical determinants, anthropometry, and clinical examination)

35. Parenteral, Enteral, and Elemental Nutrition

C. Nutrient Metabolism and Metabolic Mechanisms at the Cellular and Subcellular Levels

Categories 17-25, 14, and 27 classify research by nutrient variables; these categories should be used to indicate the nutrient variables in research classified elsewhere; and classify biochemical, subcellular, cellular, and animal research such as studies of nutrient mechanisms and metabolism not related to specific diseases, conditions, or stages of the life cycle.

17. Carbohydrates

18. Lipids (Fats and Oils)
(Includes essential fatty acids, lipo- and apoprotéins)

19. Alcohols
(Includes ethanol, sorbitols, and other alcohols used as components in synthetic and semisynthetic foods)

20. Proteins and Amino Acids
(Includes essential as well as nonessential amino acids, such as taurine and carnitine)

21. Vitamins
(Includes vitamins A, C, B_6, B_{12}, D, E, K, thiamin, riboflavin, niacin, folacin, biotin, and pantothenic acid)

22. Minerals and Essential Trace Elements
(Includes calcium, phosphorus, magnesium, iron, zinc, iodine, copper, manganese, fluoride, chromium, selenium, and molybdenum)

23. Water and Electrolytes
(Includes sodium, potassium, and chloride)

24. Fiber

25. Other Nutrients in Food
(Such as cobalt, nickel, vanadium, silicon, tin, arsenic, cadmium, choline, lecithin, and various growth factors)

***14. Nutrient Interactions**
(Includes nutrient-nutrient interactions, nutrient-drug interactions, nutrient-toxicant interactions, and nutrient toxicity)

***27. Bioavailability of Nutrients**
(Includes methods for the determination of bioavailability of nutrients)

II. Research in Food Sciences

Categories 26-29 should be used for research in the nutritional aspects of food sciences.

26. Food Composition
(Includes nutritional quality, nutrient content, and research on methods of analysis for nutrients and fiber)

***27. Bioavailability of Nutrients**
(Includes methods for the determination of bioavailability of nutrients)

28. Effects of Technology on Acceptability and Nutritional Characteristics of Foods and Diets
(Includes the beneficial and adverse effects of varietal and species differences, harvest and post-harvest technology, retail food practices, food processing, handling, preservation, and home cooking)

29. Other Research in Food Sciences

III. Research on Nutrition Monitoring and Surveillance of Populations

30. Food Consumption Surveys
(Includes research on methods for determination of food consumption and its trends, and research utilizing data derived from such surveys)

31. Studies of Dietary Practices, Food Consumption Patterns, and Their Determinants

***16. Nutritional Status**
(Includes research on methods for the determination of nutritional status and surveillance: dietary history and food consumption, biochemical determinants, anthropometry, and clinical examination)

IV. Research in Nutrition Education

Categories 32-33 encompass research in nutrition education.

32. Studies on Methods for Informing and Educating the Public About Nutrition, Health, and Dietary Practices and for Countering Nutrition Misinformation
(Includes studies on methods for informing and educating professionals in these areas)

33. Other Research in Nutrition Education

V. Research on the Effects of Government Policy and Socioeconomic Factors on Food Consumption and Human Nutrition

34. Effects of Government Policy and Socioeconomic Factors on Food Consumption and Human Nutrition

VI . NIH Special Interest Areas

Codes 51-56 have been assigned to special interest areas of the NIH.

51. Prevention of Disease

52. International Research

53. Epidemiological Research

54. Education for Professionals

55. Education for the Public

56. Clinical Trials

*Codes marked by an asterisk are applicable to more than one class.

Appendix J

NIH Award Mechanisms

The NIH relies on three major instruments for accomplishing its program goals through the efforts of scientists outside the NIH. The mechanisms are financial assistance awards (grants and cooperative agreements) and acquisition awards (contracts).

Financial Assistance Awards

Grants. Grants for health-related research projects or activities make up the largest category of funding provided by the NIH. These grants encourage and support meritorious projects or programs in all scientific fields related to health and span the spectrum from basic and applied research in laboratory and clinical settings to the evaluation, demonstration, and dissemination of new medical technologies. In addition, grants are awarded to create and sustain certain special resources or facilities for such research.

Grants are awarded to nonprofit organizations and institutions, governments and their agencies, and to individuals and for-profit organizations for the support of research in health, medicine, and allied fields. Grants provide funds for salaries, equipment, supplies, travel, and other allowable direct costs of the research, as well as for indirect costs. Through the grant mechanism, the NIH supports research projects, centers, career development, and other research programs.

Grants are used when the idea for the research or training project is initiated by the investigator; when no substantial program involvement is anticipated between the funding ICD and the recipient during performance of the activity; and when there is no expectation on the part of the funding ICD for delivery of a specified product or service. A grant may provide funds for essentially all reasonable costs of the activity. Grant applications may request, in most instances, an approximate amount of financial support and the duration of time, usually no more than 5 years, needed to complete the project. Funding is accomplished in annual increments.

Most applications for grant support originate with an individual investigator who develops a proposed plan for research or research training within an area of interest to the NIH. In addition, the NIH employs a variety of mechanisms to stimulate submission of applications in areas of high priority or special concern, including program announcements (PAs) and requests for applications (RFAs).

Cooperative Agreements. Cooperative agreements are similar to grants in that they are awarded by NIH to assist and support research and related activities. They differ, however, in that grants require minimal involvement of the awarding ICD during the performance of project activities, but cooperative agreements give a substantial programmatic, i.e., scientific/technical, role to the ICD. This role may involve cooperation or coordination to assist awardees in carrying out the project or review and approval of certain processes/ phases in the scientific management of the project.

Policies and procedures for application, review, and administration of cooperative agreements are similar to those for grants. An important difference, however, is that the unit issues a specific PA or RFA describing the program, functions, or activities that it proposes to support by cooperative agreement and the nature of the proposed staff involvement. Terms and conditions, above and beyond those required for the normal stewardship of grants, must be negotiated in order to establish the rights, responsibilities, and duties of the prospective awardee and the NIH awarding unit, based on the terms and conditions outlined in the PA or RFA.

Review Process. Applications are subjected to a peer review process that is based upon two sequential levels of review, both of which are required by law. In general, applications for various types of financial assistance awards are received and reviewed three times per year. The first level of review is performed by initial review groups (IRGs), often called study sections, composed of at least 75 percent non-Federal scientists selected for their competence in particular scientific areas. An NIH health scientist administrator serves as Scientific Review Administrator (SRA) of the review group. The task of the IRGs is to evaluate the grant application for scientific and technical merit.

In considering the scientific merit of each application, the members of the IRG assess:
- scientific, technical, or medical significance and originality of the proposed research;
- appropriateness and adequacy of the experimental approach and methods to be used;
- qualifications and experience of the principal investigator and staff in the area of proposed research;
- reasonable availability of resources necessary to the proposed research;
- reasonableness of the proposed budget and duration in relation to the proposed research; and
- where an application involves activities that could have an adverse effect upon humans, animals, or the environment, the adequacy of the proposed means for protecting against such effects.

For each application, a recommendation of Not Recommended for Further Consideration or deferral for additional information is made by majority vote. For all other applications, the IRG further discusses the strengths and weaknesses, according to the usual criteria, after which each member of the IRG individually records a numerical rating that reflects a personal evaluation of the relative scientific merit of the proposed research or training. Members are asked to base the numerical rating on an adjectival scale from 1.0, most meritorious (outstanding), to 5.0, the least meritorous (acceptable) rating, with increments of 0.1. All applications, whether given a priority rating, or Not Recommended for Further Consideration, will be included in the calculation of percentiles. With respect to research costs, IRGs are asked to scrutinize proposed budgets very carefully and closely.

After the meeting, the SRA averages the indivdual reviewer's ratings for each favorably recommended application and multiples by 100 to provide a three-digit rating that is the priority score. In addition to the priority score, a percentile rank is displayed on the summary statement of those applications reviewed by the IRG. The percentile represents the relative position or rank of each priority score among the scores assigned by the particular IRG. The percentile rank of priority scores guides the councils and institutes in their decisions about which recommended applications are funded.

The SRA prepares a summary statement for each application and forwards it to the appropriate ICD for review by its council or board. A copy of the summary statement is also automatically sent to the principal investigator by the ICD. The summary statement contains a description and critique of the proposed activity, an explanation of the recommendation of the IRG, a recommended budget, and notations about any special points such as a split vote or a potentially hazardous experimental procedure.

The second level of review of applications is made by the national advisory council or board associated with the awarding ICD. These groups are composed of both scientific and lay representatives who are chosen for their expertise, interest, or activity in matters related to the individual ICD missions. Council or board recommendations are based on judgments about scientific merit and relevance to ICD program goals. In general, the NIH may make an award only if the application has been recommended by both an IRG and a national advisory council or board.

Acquisition Awards

Contracts. NIH awards research and development (R&D) contracts to academic institutions and other nonprofit and commercial organizations for specific scientific inquiry directed towards particular areas of research and development needed by the NIH or U.S. government. In these circumstances the NIH wishes to utilize advances in knowledge and technology to search for solutions to specific questions. Contract performance is monitored closely by NIH to ensure accomplishment of contract goals for the benefit of or use by the awarding ICD, the NIH, or the government.

Most NIH R&D contracts are of the cost-reimbursement type, where the NIH pays contractors allowable, allocable, and reasonable costs in performing the project. In addition to reimbursable costs, a fee may be paid where appropriate.

The review process for solicited R&D contracts differs from that for grants in that all offerers respond to a Government-defined statement of work contained in a solicitation document called a request for proposal (RFP). Proposals responding to the solicitation are evaluated against fixed evaluation criteria specified in the RFP. Consistent with statutory and regulatory requirements for peer review of NIH solicited contract projects, the concepts of each requirement and the contract proposals are evaluated by scientific peer-review groups composed of at least 75 percent non-Federal advisors who provide recommendations regarding the merits of the basic purpose, scope, and objectives of proposed projects, and the relative merits of each proposal. In order to reach all segments of the scientific community, contract opportunities and requirements are advertised as widely as possible. Solicitation announcements appear in the Commerce Business Daily. (Subscriptions are available from the Superintendent of Documents, Government Printing Office, Washington, D.C. 20402.) Announcements of RFP availability also are published in the "NIH Guide for Grants and Contracts." Some project solicitations also may appear in scientific and medical journals or other pertinent publications.

R&D contract proposals responding to NIH solicitations undergo review by advisory peer evaluation groups whenever RFPs seek offerers for innovative and original approaches to accomplish tasks described in our solicitations. All proposals are evaluated strictly in accordance with evaluation criteria specified in the RFP. All of the tasks should be accomplished. All proposals are evaluated strictly in accordance with the evaluation criteria indicated in the RFP.

Recommendations of peer reviewers, and the results of separate NIH staff evaluations of technical and cost proposals, provide the basis for negotiations with offerers in a competitive range. At the conclusion of these discussions, offerers are requested to submit a best and final offer, which then serves as the basis for selection of offerers for award(s).

ICDs occasionally make awards in response to unsolicited contract proposals when they meet specific NIH program needs and when adequate justification exists for a noncompetitive award. In these instances, peer reviews may simultaneously evaluate both the concept and the approach for the proposed project. Subsequent evaluations and negotiations are similar to those for solicited proposals.

Clinical Trials

Clinical trials in nutrition are supported by each of the major mechanisms discussed above--research grants, contracts, and cooperative agreements. A clinical trial is defined as a scientific research activity undertaken to define, prospectively, the effect and value of prophylactic/diagnostic/therapeutic agents, devices, regimens, procedures, etc., applied to human subjects. The study must be prospective, and intervention of some sort must occur. The number of cases or patients depends on the hypothesis being tested but must be sufficient to permit anticipation of a definite, statistically significant result. Phase I, feasibility, or pilot studies are excluded by definition.

Career Development Awards

Workforce development in nutrition research is enhanced through such mechanisms as the Modified Research Career Development Awards, Academic/Teacher Awards, Clinical Investigator Awards, Physician Scientist Awards, and the Dentist Scientist Awards. Brief descriptions of these awards follow.

- Modified Research Career Development Awards foster the development of young scientists with outstanding research potential for careers of independent research in the sciences related to health.

- Academic/Teacher Awards create and encourage a stimulating approach to disease-specific curricula that will attract high-quality students, foster academic career development of promising young teacher-investigators, develop and implement excellent multidisciplinary curricula through an interchange of ideas, and enable the grantee institution to strengthen its existing teaching program. The academic and teacher investigator awards are not used by all of the institutes.
- Clinical Investigator Awards provide the opportunity for promising medical scientists (with demonstrated aptitude to develop into independent investigators) or faculty members to pursue research aspects of categorical areas applicable to the awarding unit and aid in filling the important academic faculty gap in these shortage areas within health professional institutions of the country.
- Physician Scientist Awards (Individual) support a newly trained clinician or clinically trained dentist nominated by an institution for the development of independent research skills and experience in a fundamental science.
- Dentist Scientist Awards (individual and institutional) support newly trained dentists to enhance their clinical training and obtain basic science research training.

Training Grants and Fellowships

The NIH supports the training of scientists for careers in the behavioral and biomedical sciences. Training opportunities are provided primarily through National Research Service Awards (NRSAs) and Fogarty International Fellowships.

National Research Service Awards. The major objectives of these awards are l) to increase the number of individuals trained for research and teaching in specifically designed biomedical areas, and 2) to improve the environment in which the biomedical training is conducted. NRSA awards are made to U.S. citizens, noncitizen nationals, or individuals that have been lawfully admitted to the United States for permanent residence. Several of the most common types of NRSA awards are described below.

- Postdoctoral individual NRSAs, commonly known as "fellowships," are awarded to provide postdoctoral research training to qualified individuals who have received a Ph.D., M.D., D.D.S., or equivalent degree. The award provides the opportunity to carry out supervised research to enable biomedical scientists, clinicians, and others to broaden their scientific backgrounds and expand their potential for research in health-related areas. Each applicant must arrange to work with a particular sponsor affiliated with an institution that has the staff and facilities needed for the proposed training. The institutional setting may be a domestic or foreign nonprofit, private, or public institution, including NIH and ADAMHA.
- Institutional NRSAs, commonly known as "training grants," are awarded to domestic nonprofit, private, and non-Federal public institutions to support a training program in biomedical research at the predoctoral and postdoctoral levels. The applicant institution must have or be able to develop the staff and facilities required for the proposed program, and is responsible for the selection and appointment of trainees. Institutional grants may be made for periods up to 5 years and may be renewed. However, an individual may not receive more than 8 years of support in the aggregate from an NRSA (5 years predoctoral support and 3 years postdoctoral support) unless a waiver is granted by the responsible Public Health Service agency.
- Senior fellowships are designed to provide opportunities for experienced scientists to make major changes in the direction of their research careers, to acquire new research capabilities, to broaden their scientific background, to enlarge their command of an allied research field, or to take time from regular professional responsibilities to increase their capabilities for engaging in health-related research. Investigators who hold a doctorate or equivalent degree and have had at least 7 subsequent years of relevant research or professional experience may apply for senior fellowships. The award is granted for 1 year, with continued support not to exceed 24 months contingent upon the research training plan, satisfactory progress and the availability of funds.
- Fogarty International Fellowships. To further international cooperation and health research, the Fogarty International Center provides for and administers International Postdoctoral Fellowship programs for foreign scientists to study in the U.S. and for U.S. scientists to study abroad.

Information Sources at the NIH

The "NIH Guide for Grants and Contracts" describes programs at the NIH, announces new programs, RFAs, and RFPs, and provides policy guidance. Copies of the Guide may be found in many research and medical libraries. To request the Guide or for general information on NIH extramural programs, contact:

Institutional Liaison Office
Office of Extramural Research
National Institutes of Health
Building 31, Room 5B31
Bethesda, Maryland 20892
301-496-5366

The Office of Grants Inquiries in the Division of Research Grants serves as a focal point for information on NIH grant programs and application procedures. Relevant publications and single copies of application kits (if not available at an organization's application control office) may be obtained from:

Office of Grants Inquiries
Division of Research Grants
National Institutes of Health
Westwood Building, Room 449
Bethesda, Maryland 20892
301-496-7441

Questions regarding the extramural programs of a particular ICD should be directed to the awarding unit concerned; addresses and telephone numbers of ICD nutrition program contacts are listed in section 2. In addition, the DNRC and the NCC publish a brochure entitled *Nutrition Research at the NIH* for extramural scientists and potential grantees. To obtain a copy, contact:

Division of Nutrition Research Coordination
National Institutes of Health
Building 31, Room 4B63
Bethesda, Maryland 20892
301-496-9281

ACF	Administration for Children and Families
ACRF	Ambulatory Care Research Facility
ADAMHA	Alcohol, Drug Abuse, and Mental Health Administration
ADEAR	Alzheimers Disease Education and Referral
AHA	American Heart Association
AID	Agency for International Development
AIDS	acquired immunodeficiency syndrome
AIN	American Institute of Nutrition
ALD	adrenoleukodystrophy
AMN	adrenomyeloneuropathy
AMO	azoxymethane
AOA	Administration on Aging
APHA	American Public Health Association
APPLI	Assisting Primary-care Providers in Lipid-lowering Intervention
ARAT	acyl:CoA retinol acyltransferase
ARIC	Atherosclerosis Risk in Communities
ARS	Agricultural Research Service
ASTPHNPD	Association of State and Territorial Public Health Nutrition Program Directors
ATP	adenosine triphosphate
B-FSH	bioactive follicle-stimulating hormone
B-LH	bioactive leutenizing hormone
BLSA	Baltimore Longitudinal Study of Aging
BMI	body mass index
BP	blood pressure
CARDIA	Coronary Artery (Disease) Risk Development in (Young) Adults
CATCH	Child and Adolescent Trial for Cardiovascular Health
CC	Clinical Center
CDC	Centers for Disease Control
CFSAN	Center for Food Safety and Applied Nutrition
CHD	coronary heart disease
CNRU	Clinical Nutrition Research Unit
CPRP	Cancer Prevention Research Program
CRIS	Current Research Information Service
CVD	cardiovascular disease
DDDN	Division of Digestive Diseases and Nutrition
DDE	dichlorodiphenyldichloroethylene
DDT	dichlorodiphenyltrichloroethane
DHA	docosahexaenoic acid
DHHS	Department of Health and Human Services
DISC	Dietary Intervention Study in Children
DLA	Division of Legislative Analysis
DMBA	dimethylbenz (a)anthracene
DNA	deoxyribonucleic acid
DNRC	Division of Nutrition Research Coordination
DOC	Department of Commerce
DOD	Department of Defense
DPHP	Disease Prevention and Health Promotion
DPI	Division of Public Information
DRR	Division of Research Resources
DRS	Division of Research Services

DTS	Division of Technical Services
DVA	Department of Veterans Affairs
ECG	electrocardiogram
EP	Extramural Program
EPA	eicosapentaenoic acid
EPA	Environmental Protection Agency
ERG	electroretinogram
ERS	Economic Research Service
ES	Extension Service
FDA	Food and Drug Administration
FFF	foreign-funded fellowship
FFM	fat-free mass
FIC	Fogarty International Center
FNS	Food and Nutrition Service
FOTMAC	Fish Oil Test Materials Advisory Committee
FOTMDC	Fish Oil Test Materials Distribution Committee
FOTMP	Fish Oil Test Materials Program
FSH	follicle-stimulating hormone
FY	fiscal year (October 1 through September 30)
GCRC	General Clinical Research Centers
GDS	gastric delivery system
GnRH	gonadotropin releasing hormone
GRC	Gerontology Research Center
GSH	glutathione
HDL	high density lipoprotein
HHANES	Hispanic Health and Nutrition Examination Survey
HIV	human immunodeficiency virus
HNIS	Human Nutrition Information Service
HNRIM	Human Nutrition Research Information Management
HRSA	Health Resources Services Administration
HS/HC	high salt/high calcium
HS/LC	high salt/low calcium
IBNMRR	Interagency Board on Nutrition Monitoring and Related Research
ICD	Institute, Center, Division
ICHNR	Interagency Committee on Human Nutrition Research
IGF-I	insulin-like growth factor I
IHS	Indian Health Service
I-LH	immunoactive leutenizing hormone
IND	investigational new drug
IRE	iron-responsive element
IRE-BP	iron-responsive element binding protein
IRF	international research fellowship
IRG	Initial Review Group
IRP	Intramural Research Program
IU	international unit
IVD	interactive video disc
LBW	low birth weight
LDL	low density lipoprotein
LDL-C	low density lipoprotein-cholesterol
LH	leutenizing hormone
LRAT	lecithin:retinol acyltransferase
MONICA	Multinational Monitoring of Trends and Determinants in Cardiovascular Disease
MOU	memorandum of understanding
MRI	magnetic resonance imaging

mRNA	messenger ribonucleic acid
MVP	matrix vesicle proteolipids
NAL	National Agricultural Library
NASA	National Aeronautics and Space Administration
NCC	Nutrition Coordinating Committee
NCCDPHP	National Center for Chronic Disease Prevention and Health Promotion
NCEMCH	National Center for Education in Maternal and Child Health
NCEP	National Cholesterol Education Program
NCHGR	National Center for Human Genome Research
NCHS	National Center for Health Statistics
NCI	National Cancer Institute
NCNR	National Center for Nursing Research
NCRR	National Center for Research Resources
NEC	necrotizing enterocolitis
NEI	National Eye Institute
NES	Nutrition Education Subcommittee
NGHS	National Growth and Health Study
NHANES	National Health and Nutrition Examination Survey
NHBPEP	National High Blood Pressure Education Program
NHLBI	National Heart, Lung, and Blood Institute
NIA	National Institute on Aging
NIAAA	National Institute of Alcoholism and Alcohol Abuse
NIADDK	National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	National Institute of Child Health and Human Development
NICU	Neonatal Intensive Care Unit
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIDDM	noninsulin dependent diabetes mellitus
NIDR	National Institute of Dental Research
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
NINDS	National Institute of Neurological Disorders and Stroke
NIST	National Institute of Standards and Technology
NLM	National Library of Medicine
NMFS	National Marine Fisheries Service
NNMS	National Nutrition Monitoring System
NOAA	National Oceanic and Atmospheric Administration
NPB	Nutrition Policy Board (DHHS)
NRSA	National Research Service Award
NSF	National Science Foundation
NTP	National Toxicology Program
OC	Office of Communications
OD	Office of the Director
ODP	Office of Disease Prevention
ODPHP	Office of Disease Prevention and Health Promotion (DHHS)
OPEC	Office of Prevention, Education and Control
ORS	Office of Research Services
OSTP	Office of Science and Technology Policy
PAs	program announcements

PAH	para-aminohippuric acid
PAS	para-aminosalicylic acid
PCAA	Preventive Cardiology Academic Award
PhIP	2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine
PHS	Public Health Service
PTCA	percutaneous transluminal coronary angioplasty
PTH	parathyroid hormone
PTH-rp	parathyroid hormone-related peptide
R&D	research and development
RBF	renal blood flow
RBP	retinol binding protein
RDA	recommended dietary allowance
RFAs	requests for applications
RFPs	requests for proposals
RNA	ribonucleic acid
SBIR	Small Business Innovation Research
SCAN	Study of Children's Activity and Nutrition
SRA	Scientific Review Administrator
SIF	senior international fellowship
TBHQ	tertiary butyl hydroquinone
TfR	transferrin receptor
TNF	tumor necrosis factor
TOBEC	total body electrical conductivity
TPN	total parenteral nutrition
UCLA	University of California, Los Angeles
UNICEF	United Nations Children's Fund
USDA	U.S. Department of Agriculture
UTR	untranslated region
VLCFA	very long chain fatty acids
VLDL	very low density lipoprotein
WHHL	Watanabe Heritable Hyperlipidemic
WHO	World Health Organization

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